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Incidence of aneurysm growth following endovascular aneurysm sealing of abdominal aortic aneurysms and their associations with stent movement: retrospective observational study.

Thesis by Asma Yafawi

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To my parents, Nabila Yafawi and Ayman Yafawi,

who paved the way.

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You can teach a student a lesson for a day; but if you can teach him to learn by creating curiosity, he will continue the learning process for as long as he lives.

–Clay P. Bedford

Author Declaration

I hereby declare that I am the sole author of this thesis and that information contained within it has not been presented for any other degree or qualification. This study was carried out at the Institute of Translational Medicine, University of Liverpool and at the Liverpool Vascular and Endovascular Service, Royal Liverpool University Hospital.

Abstract

Purpose. We investigated the incidence and extent of aneurysm growth after endovascular aneurysm sealing (EVAS) of abdominal aortic aneurysms (AAA), its relationship with stent movement and adherence to the instructions for use of the Nellix endograft.

Methods. In this retrospective single centre study, we reviewed clinical data and follow-up computed tomography (CT) images of patients undergoing elective infra-renal EVAS performed as a primary interventions and with a minimum follow-up of 1 year. The baseline postoperative CT scan at one month and the subsequent scans were used to measure the maximum AAA diameter, AAA volumes and the distance between the proximal end of stents and a reference vessel. AAA growth was defined as a change of ≥5mm in maximal AAA diameter and/or an increase of more than 5% in AAA volume. Device migration was based on the SVS definition of >10mm downward movement of either Nellix stent in the proximal landing zone; furthermore, we defined proximal displacement a downward movement of ≥4mm. Patients were categorised according to adherence to the old (2013) or new (2016) Nellix IFU.

Results. 76 patients were eligible for inclusion in our study. Over a 4-year period, diameter change of ≥5mm was observed in 18 patients (24%) whilst significant volume increase was observed in 50 patients (66%). AAA growth was not associated with adherence to IFU. Proximal displacement occurred in 42 patients (55%) and migration in 16 patients (21%), with similar incidence in right and left stents. Proximal displacement was significantly more frequent among patients whose anatomy did not conform to the current IFU (p=0.025). AAA growth by diameter increase, was significantly associated with both migration and proximal displacement (p=0.000 and p=0.007, respectively). AAA growth by volume increase was not associated with stent movement.

Conclusion. Infrarenal EVAS is prone to AAA growth, irrespective of IFU. The Nellix endoprosthesis may also be complicated by proximal displacement and migration, particularly when performed outside IFU. AAA growth is associated with stent movement, however it is unclear which is the cause and which is the effect.

Contents

Abbreviations

AA	abdominal aorta
AAA	abdominal aortic aneurysm
ACE	angiotensin converting enzyme
ADAM	Aneurysm Detection And Management
AUI	Aorto-uni-iliac device
ChEVAR	Chimney Endovascular aneurysm repair
ChEVAS	Chimney Endovascular aneurysm sealing
CI	confidence interval
CIA	common iliac artery
CT	Computed Tomography
Et al	et alia (and others)
EVAR	endovascular aneurysm repair
FEVAR	Fenestrated endovascular aneurysm repair
FR	French catheter scale
GP	General Practitioner
ICC	intraclass correlation coefficient
IFU	Instruction for Use
IFU-2013	Instruction for use 2013
IFU-2016	Instruction for use 2016
IHD	ischemic heart disease
IMA	Inferior Mesenteric Artery
IQR	interquartile range
L1-4	lumbar spine vertebrae number 1 to 4
MRI	Magnetic Resonance Imaging

NICE	National Institute for Health and Clinical Excellence
NSAIDs	Non-steroidal anti-inflammatory drugs
RCT	Randomised Controlled Trial
SD	standard deviation
SE	standard error
SMA	Superior Mesenteric Artery
SVS	Society of Vascular Surgery
Vs	versus
UKSAT	UK Small Aneurysm Trial
US	Ultrasound scan

List of Figures

List of Tables

Chapter 1: The Abdominal Aortic Aneurysm

1.1. Abdominal aorta

The abdominal aorta is the largest artery in the abdomen and is the continuation of the descending thoracic aorta. It is approximately 13 cm in length; it begins at the aortic hiatus of the diaphragm at the level of the twelfth thoracic vertebra and ends at the body of the fourth lumbar vertebrae (L4), where it divides into the right and left common iliac arteries.[1, 2] It is located at the posterior abdominal wall in the retroperitoneal space. The abdominal aorta is subdivided into: suprarenal/paravisceral segment which is inferior to the diaphragm but superior to the renal arteries; and the infrarenal segment which is inferior to the renal arteries but superior to the iliac bifurcation. It supplies all abdominal organs, the pelvis and lower limbs with its terminal branches. The mean calibre of the abdominal aorta diminishes in size from proximal to distal end as a result of the large vessels that branch off it; the extent of this escalates with advancing age.[3] The curvature of this vessel is described as convex as it follows the bodies of the lumbar vertebra to the left of the inferior vena cava, with the peak of this convexity corresponding to the level of the third lumbar vertebra.[4] The aortic bifurcation is usually found at L4 and the angle of bifurcation is variable.[5]

1.1.1. Abdominal Aortic Diameters

Steinberg and Stein first measured normal abdominal aortic diameters in 1965 using intravenous aortography.[6] They presented diameters at different levels for both sexes, from the level of the 11th rib to the aortic bifurcation. The range was 18.7-26.9mm in men and 17.5-24.4mm in women, with the largest value at the most proximal point and evidence of tapering as the vessel progresses towards the bifurcation. They also reported that increasing age is associated with increasing diameter, particularly after the age of 60.[7] It is well established that, between the ages of 25 to 70 years, the abdominal aorta (AA) increases in diameter by at least 25%.[8, 9] As well as age, there is a positive correlation between height and diameter.[10] Normal aortic diameters are associated with gender, with wider vessels in males.[9] The mean maximum adult infrarenal aortic diameter measured by computed tomography (CT) is 19-21mm in men and 16-18 mm in women.[11] There is evidence of ethnic variation of diameters found in the literature. [12-15] Needleman et al presented diameters collected using ultrasound which equated to a comparable 20 mm in men and 17 mm in women (SD 2.5 and 1.5 respectively).[3]

1.1.2. Aortic wall

The physiological aorta is profoundly elastic in nature and its wall is made of three layers, from the innermost: tunica intima, tunica media and tunica adventitia. The tunica intima is made of a single layer of endothelial cells supported by elastin-rich collagenous tissue. This is followed by the sub-endothelial tissue which consists of myo-intimal cells dispersed within it; these cells are comparable in composition to smooth muscle cells. Lipids can accumulate here and atheroma can arise within this layer. The tunica media is made of concentric sheets of elastin, collagen and a small number of smooth muscle cells. The tunica media is the layer that undergoes the most prominent changes in aneurysmal disease, with denser collagen fibres making the wall thicker and less pliable. The outermost tunica adventitia comprises of collagen with diffusely distributed elastin fibres.[16]

Collagen and elastin play vital mechanical roles in the aorta. Collagen expands by a limited percentage of 4% of its original state and it grants the aorta tensile strength to prevent over-distension, especially at high pressure. Elastin is able to expand by 50-70% of its original length and enables an even distribution of stress in the wall.[17] At low pressures elastin bears most of the stress/pressure load on the aortic wall maintaining the equilibrium between mural haemodynamic stress and the resultant deformation.

Differences in the physiological mean thickness of the aortic wall have been identified, within different groups of age, gender and ethnicity.[18] Thickness of the different layers of the AA within normal subjects have not been studied extensively with normal values not well established.[19] Restrepo et al microscopically measured the intima wall thickness of 2472 healthy subjects aged 15-64 which were 0.10 mm for men and 0.09 mm for women.[20] Astrand et al reported a mean intima media thickness of 0.73 mm (SD = 0.15) for men and 0.73 mm (SD = 0.16) for women using B-mode ultrasonography.[21] Arthur et al assessed aortic wall thickness using magnetic resonance imagining (MRI) in subclinical cases. MRI identified that men had significantly greater mean wall thickness (2.32 vs 2.11 mm, p = 0.028) and maximal wall thickness (3.85 vs 3.31 mm, p = 0.010) than women.[19]

1.1.3. Relations[2]

The AA is covered, *anteriorly,* by the lesser omentum and the stomach, behind which are the branches of the celiac artery and the celiac plexus; below these, by the splenic vein, the pancreas, the left renal vein, the inferior part of the duodenum, the mesentery, and aortic plexus. *Posteriorly,* it is separated from the lumbar vertebra and intervertebral fibrocartilages by the anterior longitudinal ligament and left lumbar veins. On the *left* side the left ceoliac ganglion, the ascending part of the duodenum and portions of the small intestine can be found. On the *right side* it is in relation above with the azygos vein, cisterna chyli, thoracic duct, and the right crus of the diaphragm—the last separating it from the upper part of the inferior vena cava, and from the right ceoliac ganglion; the inferior vena cava is in contact with the aorta below. On the *left side* are the left crus of the diaphragm, the left ceoliac ganglion, the ascending part of the duodenum, and some coils of the small intestine.

1.1.4. Branches

The branches of the descending aorta are described as arising and coursing in three main 'vascular planes':

1. Posterolateral: paired parietal
2. Anterior midline: unpaired visceral
3. Lateral: paired visceral

Paired parietal branches of the aorta supply blood to the diaphragm, posterior abdominal wall vertebral column, vertebral canal and its contents.[3, 22] The anterior midline visceral plane first gives off the ceoliac trunk immediately below the diaphragmatic hiatus. One cm below the origin of the coeliac trunk, the superior mesenteric artery (SMA) originates at the level of the 1st to 2nd lumbar intervertebral discs (L1-L2). The inferior mesenteric artery (IMA) branches off from the anterior or left anterolateral aspect of the AA, approximately 3 cm above the aortic bifurcation at the level of 3rd Lumbar vertebrae disk (L3). The paired renal arteries just below the SMA with the right branch originating slightly higher. Inferior to the renal arteries is where the gonadal arteries originate. The median sacral artery, an unpaired branch, may be said to occupy a forth (posterior) plane because it arises from the posterior aspect of the aorta, just above the aortic bifurcation.[23] There is well established evidence of a vast variation in the morphology of the AA and its branches which occur at the early stages during embryological development[24-26]

1.2. Abdominal Aortic Aneurysm

1.2.1. Definition

The term aneurysm is derived from the ancient Greek and means 'a widening'. It is defined as a permanent localized arterial dilation of at least 50% of what is deemed normal and involving all three layers of the artery.[27] Pseudo-aneurysms, also known as false aneurysms, occur when the widening does not involve all three layers of the artery; they form as a result of a rupture of the arterial wall and formation of a perivascular haematoma.[28]

Abdominal aortic aneurysm (AAA) is a condition in which the abdominal segment of the aorta below the diaphragm becomes weakened and balloons outwards. Aneurysmal dilatation of the aorta is commonly found below the renal arteries.[29] However, expansion can also be found in the suprarenal segment, can extend upwards into the thoracic segment of the aorta above the diaphragm and downwards beyond the aortic bifurcation into the common iliac arteries.[30, 31]

Various recommendations regarding what constitutes an AAA have previously been published;[32, 33] a widely used diameter threshold is 30mm.[34] Due to the known physiological variation between different groups, as previously described, this has been challenged by some who suggest that an individualised comparison of the maximum diameter to the proximal segment should be considered.[35, 36] The Society of Vascular surgery (SVS) recommends the use of multifactorial evaluation: site, aetiology and clinical-pathological manifestations.[36]

1.2.2. Epidemiology

AAA predominately manifest in men aged 65 or over, with prevalence in this cohort ranging from 4.5% to 7.7%.[37-42] Age has been reported to be the strongest risk factor, with the prevalence rising from 2.6% to 9% between ages 60-64 years and >75 years in men.[43] Women are 3-4 times less likely to develop this disease,[44, 45] however, when diagnosed, they have higher rupture, growth and operative mortality rates when compared to men.[44, 46-49] The reasons behind the difference in incidence between the genders is not well understood, but is thought to stem from the same physiological mechanisms that govern the lower rate of atherosclerotic disease in premenopausal women.[50] Epidemiological differences between different ethnicities also exist, with Caucasian groups expressing the highest levels of AAA and the Asian population the lowest.[51, 52]

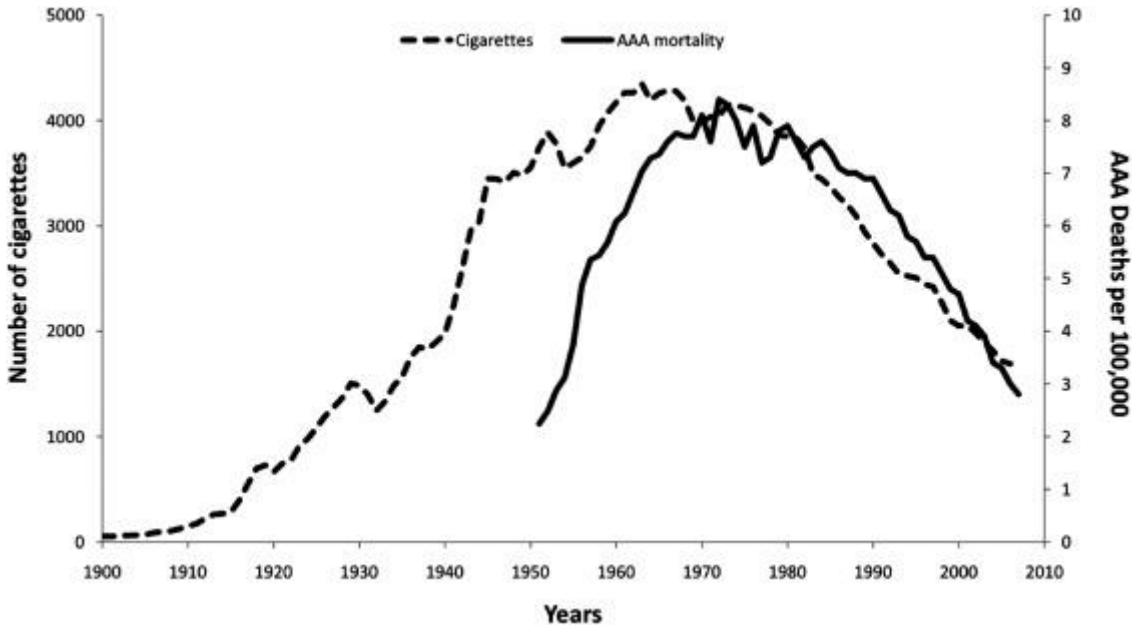
The incidence of AAA presentation in England and Wales increased until the late 1980s but has since declined.[53, 54] This decline is thought to be due to a changing epidemiology,[54] with this alteration attributed to public health campaigns as a primary prevention and better management of contributing diseases such as hypertension and hypercholesterolaemia.[55 56] Other studies corroborate with these findings.[15, 56, 57]

Each year in England and Wales, AAAs cause over 4000 deaths following aortic rupture,[58] with approximately 8000 patients a year undergoing surgery to prevent this.[59] However. The age-standardized AAA mortality rates have recently been reported to decline by 5.03% every year, this is thought to be as a consequence of the screening programme introduction.[60]

Smoking and other risk factors

Smoking is possibly the strongest environmental factor linked with the incidence and prognosis of the disease, with this association being stronger than that between smoking and cardiovascular disease.[61-65] The odds of a smoker having an AAA of 4 cm or greater, when compared to a non-smoker are as high as 5.57 [95% confidence interval (CI) 4.24 to 7.31].[66] Additionally, smoking has been found to escalate the progression of the disease and with that the rupture rate.[67] Other studies have shown that there is a significant association of disease progression with the duration of smoking exposure and the time since smoking cessation.[62] Lederle et al identified that cigarette consumption in American adults was proportionate to the decrease in deaths from ruptured AAA (Figure 1.1).[58]

Figure 1. 1 Cigarette consumption and age-adjusted AAA deaths per 100000 white men per year in the United States.[58]



Other potential risk factors include increased height, hypertension, high cholesterol, and decreased lung function. However, these associations are inconsistent within the literature.[66, 68, 69] Diabetes mellitus has been found to decrease the incidence of AAAs,[66, 70] and this is especially notable considering that the prevalence of diabetes is higher in the Asian population relative to the Caucasian population.[71] Additionally, diabetes has been linked with slower AAA growth rate.[67]

1.2.3. Detection, screening and surveillance

There are many different screening methods for AAA, of these, B-mode ultrasonography is widely accepted as the standard, as it presents a high level of sensitivity (94% to 100%) and specificity (98% to 100%).[72-77] It is non-invasive, inexpensive and does not expose the patient to any radiation. Although CT is also highly sensitive and specific as a screening modality for AAAs, it is not used as a first line option as it exposes the screened individual to radiation and is comparatively expensive.[73, 78] It is noteworthy, that whilst there is a significant correlation between diameters measured by either method, there is also a certain variability.[79, 80]

The UK National Health service AAA screening programme (NAAASP) completed its launch in 2013.[81] Its introduction was based on the results of the multicentre aneurysm screening study (MASS) and the Danish Virborg trial.[38, 82, 83] These studies showed that a single ultrasonography appointment at the age of 65 years resulted in a reduction in AAA related mortality. AAA screening remains cost effective to a prevalence of 0.5%.[84] Results of the screening programme are promising.[85, 86]

In the United Kingdom (UK), between 2015 and 2016, 2549 men were diagnosed with AAAs of 227,543 screened (1.1%). However, only 723 of them (0.3%) had AAAs large enough (at least 55 mm) to require referral for surgical consideration.[87] Many subjects with screen-detected AAAs do not require immediate treatment and are therefore enrolled into ongoing surveillance.[88]

1.2.4. Medical therapy

Numerous medical therapies for the prevention and treatment of AAA have been proposed, however, the evidence behind these has been insufficient and inconsistent. Anti-hypertensive therapy has been evaluated, as hypertension was found to be strongly associated with the disease.[89] Beta-blockers were amongst the first to be assessed, initially with encouraging results,[90, 91] which did not translate convincingly when tested on the affected population.[92] Angiotensin converting enzyme (ACE) inhibitors were also studied,[93-95] however AAA rupture and growth rate have not been shown to reduce with their use.[89, 96] Other evidence points towards this treatment having a harmful effect.[97, 98] Non-steroidal anti-inflammatory drugs (NSAIDS) have been linked with reduced AAA growth,[99] however this finding is inconsistent in the literature.[100]

Trials have investigated the impact of antibiotics on the progression of AAA. Although there have been some encouraging results on small samples, larger studies are needed to confirm any benefit.[101-103]

The most promising evidence for the potential treatment or decreased progression of AAA is perhaps that on statins.[100, 104] The mechanism by which this occurs is unknown, especially since high levels of lipids have not been linked with AAA.[67, 105] One study, which set out to investigate this trend further, was closed pre-maturely due to the low number of participants.[106] It was also deemed unfeasible and unethical to conduct randomised control trials (RCTs) on a population with many subjects having an independent indication to statin therapy, as the comparative group would need to be statin-free.

A recent systematic review and meta-analysis investigating the impact of various medical therapies on growth rates of AAA demonstrated little evidence for reduction in growth rates across a range of pharmaceutical products, but supported statins as the only therapy to show encouraging results, with a pooled difference in growth rate of –2.97mm/year (95% CI –5.83 to –0.11mm/year) between patients prescribed statins and control.[107]

1.2.5. Open surgical repair

Dubost et al published the first case of open repair of AAA in 1952.[108] During open repair, the AAA is exposed using a transperitoneal or retroperitoneal approach, a clamp is placed on the aorta above the AAA, which is then opened and a graft made of synthetic material, usually Dacron, sutured into place. The extent of arterial replacement is dependent on the extent of aneurysmal disease. In most cases, a single graft tube is sutured into place, however with moderate to severe dilation at iliac system a bifurcated graft is inserted beyond the aortic bifurcation. On completion of the repair, the AAA is loosely closed over the newly inserted graft.

This is a major operation and bears a significant risk of operative mortality and morbidity. Elective open repair results in better outcomes when compared to emergency repair, which has mortality rates of 30% -60%.[109-111] The UK National Vascular Registry Report of 2017 reported a mortality rate of 2.9%,[112] whilst the US Aneurysm Detection And Management (ADAM) trial reported a mortality of 2.7%.[113] National outcomes of 30-day operative mortality in the United Kingdom were as high as 12% in district hospitals.[114] It has been suggested that complications of open AAA repair are under-reported; Medicare data in the USA showed complication rates up to 10% at 4 years.[115] However, late complications are still thought to be infrequent and long term follow-up is not felt to be necessary.

1.2.6. Endovascular aneurysm repair

In 1991, both Parodi et al in Argentina and Volodos et al in Ukraine were the first to describe elective endovascular aneurysm repair (EVAR) of AAAs.[116, 117] EVAR was a revolutionary breakthrough for AAA therapy as it moved away from the major open surgical approach and marked the start of the evolution of the more refined endovascular therapy available to patients today.[118] This evolution was made possible with advances in patient selection, implantation technique and endoprosthesis design.[119] In 1994 the first EVAR procedure in an emergency setting was described,[120] with EVAR now resulting in lower mortality when compared to open repair.[121-127]

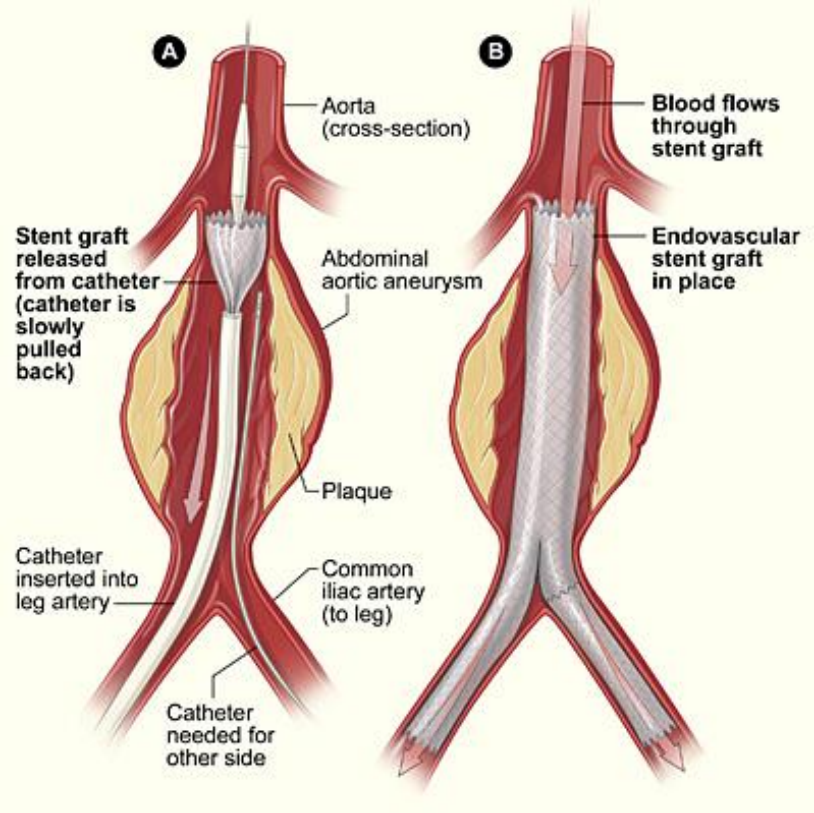
EVAR has surpassed open repair as the most common technique for treatment of AAA.[128] Despite this, anatomical constraints still exist and not all patients can be treated with commercially available infra-renal devices. Establishing suitability for EVAR is a complex process and is dependent on manufactures instructions for use and the surgeon's clinical judgement. The current literature presents varying degree of suitability of EVAR, ranging from 25% to 75%.[129-135] Fenestrated and branched graft designs have recently emerged to treat more complex and challenging anatomy with promising early results, but these grafts are expensive and require complex implantation procedures, with higher mortality and morbidity when compared with standard infra-renal EVAR.[136-140]

The procedure

EVAR has become less invasive over the years, as it is now most commonly performed using a fully percutaneous approach, where previously small incisions in each groin were needed to expose the femoral arteries for device deployment. Intra-operative fluoroscopy provides visual information on the location of the graft throughout its journey to the AAA and during implantation. The graft is positioned in the correct place using guidewires and catheters. This does expose the patient to relatively high doses of radiation and infra-arterial contrast agents which are not needed during open surgical repair.

EVAR stents are anchored to normal arterial segments both proximally (infra-renal aortic neck) and rely on radial force in the iliac arteries for seal and fixation. This is made possible by two main mechanisms: the first is through the use of hooks or barbs; the second is the radial force exerted by oversized self-expanding sealing stents at the landing zones (Figure 1.2). To ensure a stabilised device, fixation must overcome distraction forces generated by the inflowing circulation.

Figure 1. 2 Endovascular Aneurysm Repair



(A) Unsheathing of the stent after optimal positioning within the AAA, using catheters

(B) Visual representation of the EVAR device after competition of implantation

EVAR outcomes

Mortality rates post-EVAR is lower than with open repair, and is reported at 0.4% in 2017.[112] Furthermore, patients have an overall shorter hospital stay following EVAR.[132] EVAR is less than 30 years old; there is thus a degree of uncertainty regarding the long-term durability of the grafts; late complications appear to be more frequent than after open repair.[141] The EVAR 1 trial has shown that the long-term outcome of EVAR may be inferior to that of open surgery,[142] a real concern due to the rapidly growing life expectancy in the western world. Most clinicians will thus follow-up patients indefinitely post-EVAR. Surveillance imaging modalities include duplex ultrasonography, plain radiography and CT.[143, 144] The problem of late failure of EVAR has not been satisfactorily addressed so far, and is partly responsible for the comparatively high costs of the technique.[145] (Detailed rates of complications bellow)

Chapter 2: Endograft related Complications

2.1. Endoleaks and endotension

2.1.1. Definitions

White et al first proposed the concept of endoleak in 1996.[146] He defined endoleaks as blood flow outside the lumen of the endoluminal graft, but within the AAA.[147] Endoleaks arise due to incomplete exclusion of the AAA from the circulation. Some of the causes include: incomplete seal between the endograft and the wall of the blood vessel, an inadequate connection between components of a modular endograft, fabric defects or porosity, or retrograde blood flow from patent aortic side branches.[147, 148] EVAR has been reported to be complicated by endoleaks in up to 25% of cases.[149-151]

2.1.2. Classification of endoleaks

2.1.2.1. Timing[147]

When an endoleak occurs during the 30-day postoperative period, it is defined as a primary endoleak; detection beyond 30-days implies a secondary endoleak. When an endoleak re-appears after resolution (spontaneous or with help of intervention) it is known as a recurrent endoleak.

2.1.2.2. Type I endoleak

A type I endoleak develops due to an incomplete seal at the proximal aortic attachment site (type IA), at the distal iliac attachment site (type IB) or at the site of an iliac occlude, in patients treated with aorto-uni-illiac endografts (type IC). Short, severely angulated, reverse tapered, calcified and diseased necks are more prone to type IA endoleaks. Neck morphology has also been shown to predict this type IA endoleak, with evidence suggesting a neck diameter of > 28 mm significantly increases its incidence.[152] Type I endoleaks imply a persistent or recurrent risk of rupture, as the AAA remains exposed to systemic arterial pressure.[153-155]

Although small intra-operative type I endoleaks may resolve spontaneously, the SVS recommends that, if identified intraoperatively, surgeons should make every attempt to treat them prior to

procedure competition. This is commonly done using balloon moulding of the proximal seal zone, proximal extension cuffs or endostaples.[156] The latter has also been reported to reduce the risk of stent migration (see below).[156, 157] Specific treatment for type IA endoleaks also include embolization with coils or glue,[158, 159] proximal extension with visceral chimneys (ChEVAR),[160] and using fenestrated endovascular aneurysm repair (FEVAR).[161] ChEVAR and FEVAR allow the proximal seal zone of the stent to extend above the renal arteries, whilst preserving the flow into the renal arteries. Type IB endoleaks may be treated with distal extensions.[162, 163]Conversion to open repair may be necessary in patients with persistent type IA endoleak.[136]

2.1.2.3. Type II endoleak

Type II endoleak is attributed to retrograde flow from AAA side branches such as the lumbar arteries or IMA.[164-166] This is the most common endoleak, present at the time of repair in up to 25% of cases, although more than half will spontaneously resolve.[153, 158, 159, 167] At 6 months, 10% to 15% of EVAR patients have this type of endoleak.[168-170] Important risk factors include number and diameter of patent lumbar arteries, a patent IMA and anticoagulation.[171-173]

Exclusion of type II endoleaks can be achieved with embolization of the vessel with coils or glue,[159] direct translumbar injection of the AAA sac,[174] trans-caval embolization,[175, 176] and laparoscopic ligation.[177] More than half of treated type II endoleaks persist, leading to multiple procedures and occasionally open conversion.[178, 179] Other treatment options include over-sewing of the affected arteries whilst preservation of the stent.[180-182]

A type II endoleak may on occasion only be detected 6 months postoperatively or later. These endoleaks are particularly associated with AAA growth.[183] However, they rarely lead to rupture and when they do they are often associated with a type I endoleak. Surgeons anticipate this when there is a maximum AAA diameter increase in size by 5 mm or more.[184, 185] EVAR AAA growth rates are reported to occur in 18.3% of patients.[186]

2.1.2.4. Type III endoleak

Type III endoleaks usually occur due to a defect in the graft. This can arise due to incomplete seal between components and graft separation (IIIa) or due to a hole in the fabric (IIIb).[187] This causes re-pressurisation of the AAA cavity by the systemic pressure, and therefore it bears a significant risk of rupture. Treatment is necessary and is dependent on the site and cause of the endoleak.[153]

2.1.2.5. Type IV endoleak

A type IV endoleak is a leak due to fabric porosity. This rarely requires treatment as it seals spontaneously.[188] Type IV endoleaks are unlikely to occur with modern endografts.

2.1.2.6. Type V endoleak/Endotension

Endotension is AAA enlargement without a detectable endoleak. Causes include undetectable endoleak due to limited or inadequate imaging modality,[155, 189, 190] pressure transmission through thrombus or endograft fabric,[191-194] or accumulation of a serous ultrafiltrate across a microporous fabric.[195] It is now well established that AAA can continue to grow after endovascular repair with absence of a detectable endoleak.[190, 192, 196-198] Type IIIb endoleaks are very difficult to diagnose and are thought to be responsible for a portion of cases of endotension. Management is individualized and can entail observation, empirical relining of endografts (to treat suspected type IIIb endoleaks) or conversion to open repair.

2.2. Stent movement

Different terms have been used to report stent movement for the EVAR device in the literature. In 2002 the SVS used the term stent migration and defined it as movement of '>10mm relative to anatomical landmarks or any migration leading to symptoms or requiring therapy'.[199] Greenberg et al added a definition for device migration as any movement of more than twice the reconstructed resolution of the CT scan.[200] When deciding between the SVS definition and this definition, Greenberg et al suggests that clinicians should choose whichever value is lower.[200] Greenberg et al accepts the SVS definition and suggested a fixed anatomical landmark which was embraced by the vascular community.

Stent movement can occur at the proximal side or the distal side of the stent. At the proximal end of the stent the fixed anatomical landmark was defined as the SMA, whilst at the distal end it was the hypogastric artery and the aortic bifurcation. The direction of movement of the stents is categorised as cephalic or caudal. Caudal stent movement is determined by a plus sign (e.g. 11mm) and movement in a cranial direction is indicated using a minus sign (e.g.-11mm).

Stent movement occurs most frequently in the caudal direction at the proximal end of the endograft. This movement towards the AAA may lead to a type IA endoleak. Cranial stent movement at the distal landing zones may arise due to aortic remodelling and can lead to type IB endoleaks. Device migration is a late complication with its onset commonly reported 2 years post-operatively.[201-203] EVAR has been reported to be complicated by device migration in 1-10% of cases.[204-206] Causes of stent migration include incomplete device fixation, an anatomically hostile neck and progressive aortic dilation/elongation.[201, 207-209]

Management of migration in the caudal direction is dependent on anatomical features such as the quality of the aortic neck (seal zone) and aortic neck length. Treatment options include conversion to open repair and proximal extension (with or without chimneys or fenestrations).[161, 210]

Figure 2. 1 Endograft migration[211]

(A) Lateral radiograph 1 month post-EVAR, stents and vertebrae visible; (B) the intraoperative digital subtraction angiography at the time of endograft placement; (C) lateral radiograph 2 years post-EVAR - endograft limbs are bowed anteriorly suggests marginal movement; (D) the distal ends of the iliac limbs have cephalic migration, arrows point at a resultant type Ib endoleak.

2.3. Limb occlusion

One fourth of all arterial reinterventions after open repair are due to limb occlusion.[212] Risk factors include female gender, grafts extending to the external iliac arteries, associated occlusive disease and non-supported limbs.[213] Patients typically present with claudication or severe acute ischemia.[214, 215]

The EVAR 1 trial revealed that bifurcated surgical grafts are less likely to occlude vessels than AUI endograft devices.[141] The incidence of limb occlusion post-EVAR is approximately 4% (median follow-up 1.7 years (range 0-4.6 years)), with a great proportion presenting by 2 months post-EVAR and close to all within the first year.[216-218]

Chapter 3: Endovascular Aneurysm Sealing

3.1. Device description and implantation procedure

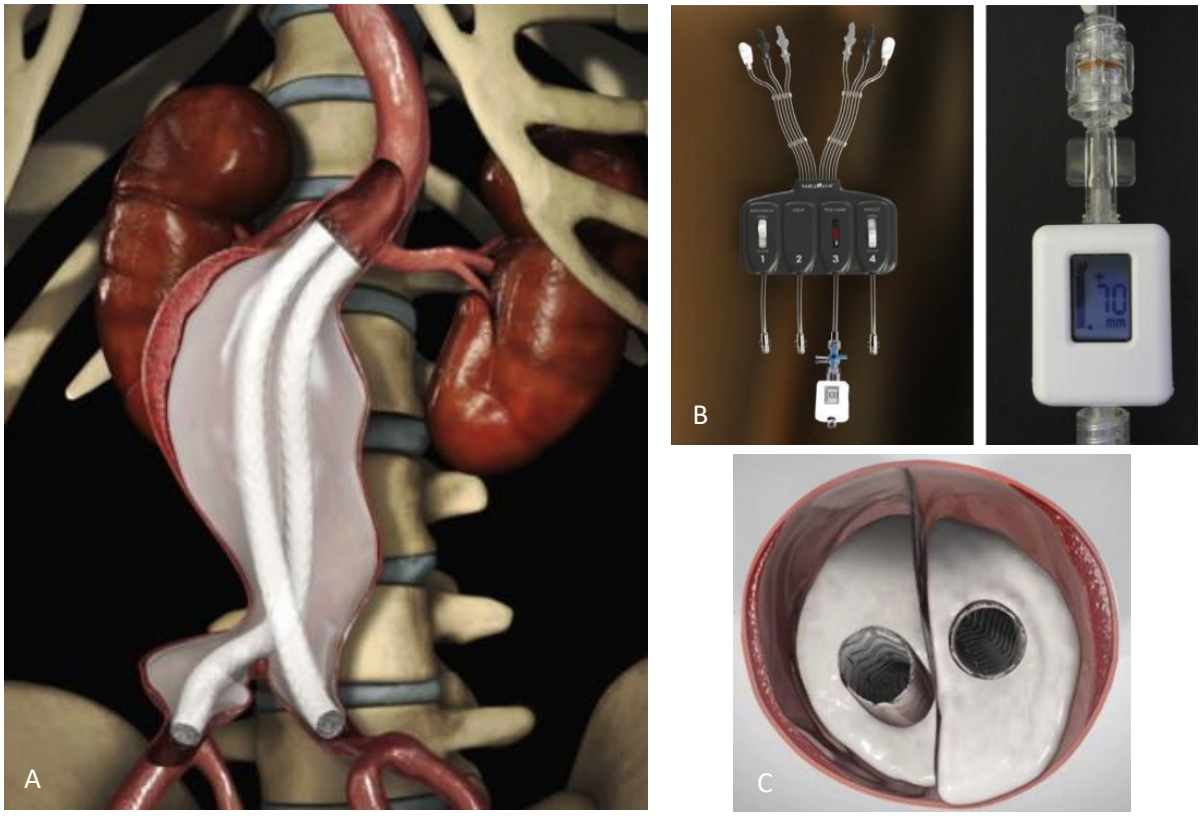
Endovascular aneurysm sealing (EVAS), which, presently, can only be performed with the Nellix endograft (Endologix Inc., Irvine Ca., USA), is a novel endovascular treatment of AAAs. The endograft received Conformité Européenne marking in April 2013 and was subsequently introduced into clinical practice.[219-221]

Its innovative design is made up of one console and 4 separate components per stent: a 17 Fr delivery catheter; a 10mm balloon expandable cobalt-chromium stent; a non-porous polytetrafluoroethylene (PTFE) endobag which surrounds the stent and a bio-compatible polymer (polyethylene glycol diacrylate hydrogel) which, once injected, is contained within the endobag (Figure3.1).

Bilateral percutaneous or surgical femoral approach is used to allow 0.35 inch guidewires to be introduced through each femoral artery and advanced into the thoracic aorta. The Nellix devices, one on each side, are then advanced over these guidewires and positioned in the aortic neck. The stents, which extend into the common iliac arteries distally, are then unsheathed using the pin and pull technique. The console, which is attached to the caudal end of the device, enables simultaneous inflation of the balloon expandable stents and the injection of polymer into the endobags at supra-systolic pressure, which mould to the AAA sac lumen and provide a complete seal proximally and distally. As the endobags fill with the polymer, which can be mixed with contrast agent for visibility under fluoroscopy, the console monitors filling pressure to a target of 180 to 220 mm-Hg, at which the seal is normally achieved. Once the endobags are filled with the polymer liquid it takes under 5 minutes at 37 degrees Celsius (°C) for the polymer to completely cure and harden to a rubbery consistency, sealing the AAA sac. During the curing time, the polymer turns from translucent to opaque white. Throughout the procedure, the endoprosthesis is visualised under fluoroscopic guidance, with angiography to assess stent position and patency of renal vessels.

Advances to the EVAS procedure include the introduction of the 'prefill' method. Before polymer introductions the endobags are filled with saline to the target pressure, to accurately estimate the polymer fill volume and to assess device stability during endobag filling. Additionally it allows, if needed, the repositioning of the device after prefill aspiration. Contrast can also be added to the saline solution to allow visualisation of the endobags.

Figure 3. 1 EVAS device[222]



(A) Animated view of the Nellix device after implantation

(B) The Nellix console, with view of the pressure monitor

(C) Animated cross-sectional view of the device within the AAA during polymer filling

3.2. Device stability

The sac-anchoring nature of the graft aims to preclude any movement of the stent. Once cured, the polymer exerts no radial force on the aortic wall: it stays in place by obliterating all space into which it could move, leaving no space within the AAA to be filled by endoleaks. While conventional endografts have a proximal and distal attachment zones for fixation, the Nellix endoprosthesis does not have any active fixation mechanism (hooks, barbs, radial force).

EVAS also relies heavily on the assumption that the AAA and the thrombus contained in it do not change after implantation. Any such change could result in device displacement, potentially leading to endoleak and rupture. Depressurised AAAs treated by EVAR or EVAS should not grow in time, hence post-EVAR AAA growth, which is known to occur in a proportion of patients, is taken as a sign of failure to exclude the AAA from the systemic circulation. For EVAS patients, a change in the volume of the AAA and the thrombus contained in it, may result in movement of the stents, leading, potentially, to endoleak and rupture. AAA growth post EVAS has not been widely reported but may have worse consequences than those seen in EVAR, given the lack of active fixation by the Nellix endoprosthesis and its known reliance on the lack of anatomical change post implantation.

3.3. Instructions for use

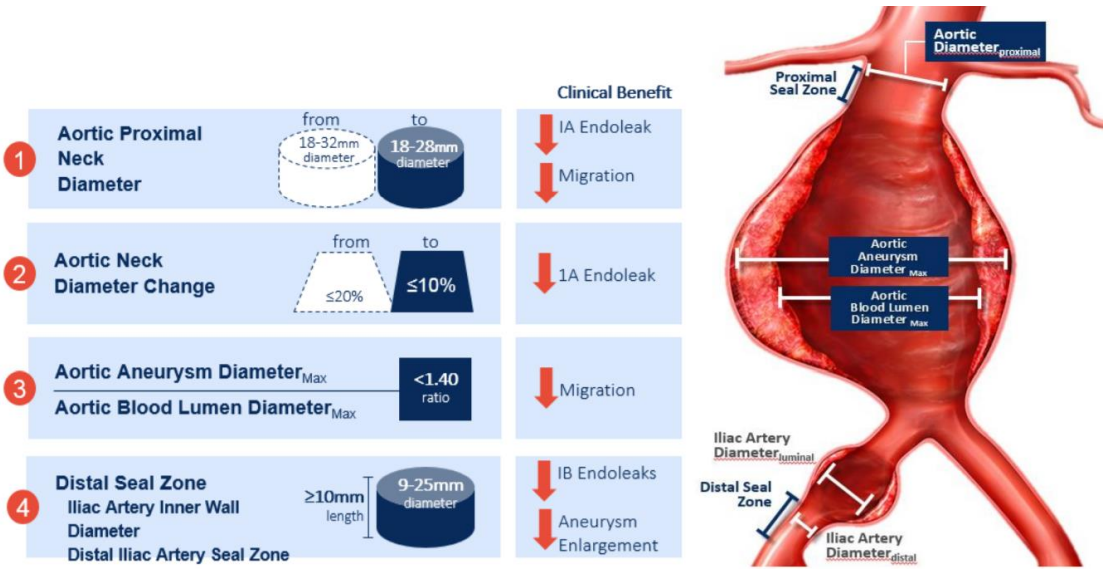
Despite the fact that the device had instructions for use (IFU), its adaptable concept, led many clinicians, during the early use of the device, to believe that treating patients beyond these instructions was in fact possible and safe.[223, 224] There was a certain perception that, the use of endobags which conform to any anatomy, made Nellix widely suitable. This included AAAs with a short or no neck, as the neck was no longer necessary to stop flow in the AAA at the time of implantation. However as complications arose this changed.[225] The EVAS FORWARD Global Registry reported that 37% of patients were in fact treated outside of IFU.[226]

Early outcomes dictated a change in the instructions for use (IFU) in October 2016 (Table 3.1),[227] which included modifications aimed specifically at reducing the occurrence of migration and AAA enlargement (Figure 3.2).[228] The old IFU allowed for a greater morphological applicability than EVAR, and with that expanded the proportion of treatable patients with AAA.[229] The new IFU removed this advantage.

Table 3. 1 IFU-2013[230] and the modified IFU-2016[228]

IFU-2013	IFU-2016
Iliac and femoral artery access that allows for atraumatic device introduction	No Change
Aortic proximal neck diameter range of 18 to 32mm	Aortic proximal neck diameter range of 18 to 28mm
Minimum aortic proximal neck length of ≥ 10mm	Criteria remains the same; however, the definition of aortic proximal neck length is updated to diameter change of 10% vs. previous 20%
Proximal aortic neck angulation of ≤60°	No Change
Aortic aneurysm with a blood lumen diameter of ≤70mm	No Change
N/A	Ratio of maximum aortic aneurysm diameter to maximum aortic blood lumen diameter <1.4
Iliac arteries luminal diameter range of 9 to 35mm	• Iliac artery blood lumen diameter range of 9 to 35mm outside the distal seal zone • Distal seal zone: length of ≥ 10mm and diameter range of 9 to 25mm

Figure 3. 2 Refined Nellix IFU[228]



3.4. The challenges

Van Noort et al showed that precise positioning of the EVAS device in the aortic neck may be difficult.[231] This study suggests that, despite operator experience, only half of the proximal sealing (landing) zone in the aortic neck is used, on average. They recommended that the stent should be positioned 5 mm above the lower boundary of the renal arteries instead of below, as the endobags often present with shoulders (a rounder rather than flat top almost perpendicular to the axis of the stent-graft frame) which causes loss of aortic neck seal (figure 3.3). This implies that the device, at its present used, can produce a tenuous seal in short necks, which may potentially be lost with minimal stent movement. On this basis, if minimal movement of the prosthesis occurs, failure may be inevitable. In addition, if the device is used in shorter necks (10mm or more), seal may not be achieved at the time of implantation, despite absence of a visible endoleaks.

The post-operative visualisation of type Ia endoleaks after implantation of the Nellix device can be difficult as the polymer within the endobags is commonly radio dense, especially during the early follow-up period.[232] Van den Ham et al set out to classify endoleaks post-EVAS in a multi-centre analysis including 1851 patients (median follow-up 1.4 years ± 0.78 years). They acknowledged that there is a possibility of AAA pressurisation in the absence of visible endoleaks heralded AAA growth (by volume or diameter), thrombus volume growth, new thrombus between the endobags, endobag separation or any movement of one or both endobags or stents.[233]

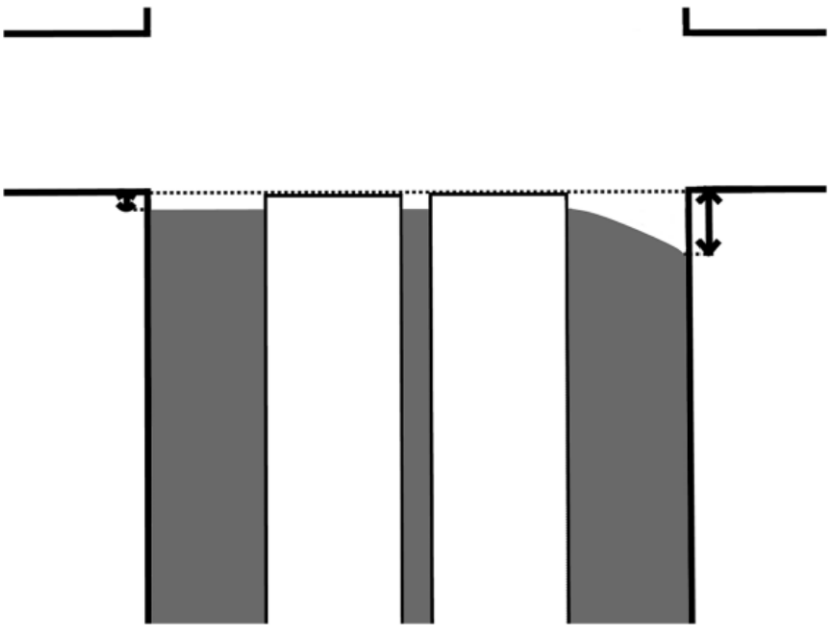


Figure 3. 3 Schematic representation of the Nellix in the infrarenal AA. Example of differences between the top of the stent frame and the top of the left endobag (flat shoulder) and right endobag (drooping shoulder).[231]

3.5. EVAS outcomes

Thirty-day outcomes

Brown et al demonstrated satisfactory early outcomes of EVAS in a recent systematic review of 11 studies, which included 684 patients.[234] 30-day mortality rate was 2.6 % in the full cohort and 1% for elective patients. At 30-days endoleaks were noted in 4.7% of all patients and 4.8% in elective cases. 30-day AAA related re-intervention rate was 5.7% and 4.6% in the full cohort and elective patients, respectively. These promising early outcomes are consistent within the literature, including the EVAS FORWARD Global Registry.[226, 235]

Mid-term and long term outcomes

Long term follow-up data is limited within the current literature. Stenson et al recently reported midterm results (up to 3 years) of the EVAS devise which included the comparison of the different IFU groups.[236] Just under 25% of their patient cohort (150 patients) underwent re-intervention, 14 % of patients had a type 1 endoleak and secondary rupture was reported in 4.7% of patients. The study concluded that when adhering to IFU the device has acceptable results, particularly with respect to migration (>5mm).[236] Migration was identified in 5.3% of patients. England et al identified migration (≥4mm) in 28% of patients at one year.[237] Boeckler et al also reported Type Ia (3%), type Ib (2%), and type II (2%) endoleaks in a recent multicentre case series (171 patients).[238]

Argani et al developed a mathematical model that encompasses the forces that act on the sealed AAA: both static and dynamic.[239] These include Eigen-frequencies which are as a result of the elastic properties of the device and may be initiated by external means, such as walking, running and using different means of transport etc. This study suggests that static forces and vibrations elicited from daily activities may lead to stent movement and, potentially, migration and endoleaks.

3.6. EVAS in Liverpool

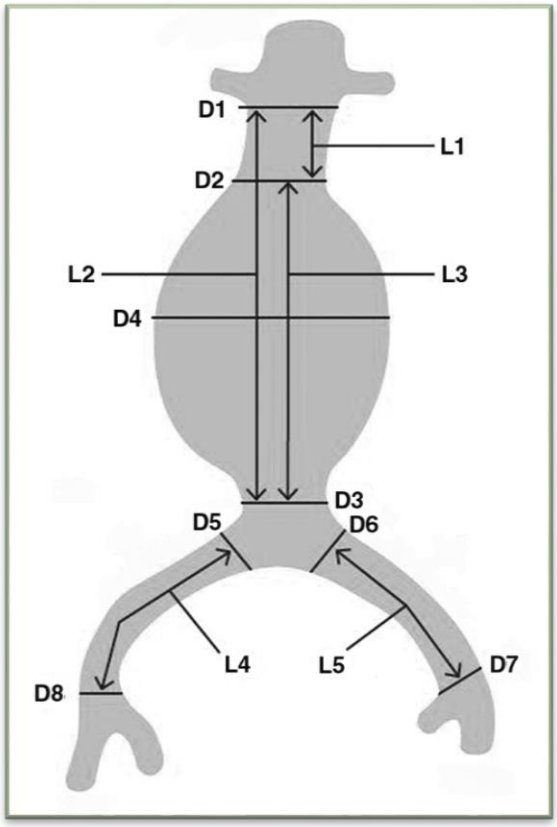
Patient management

EVAS was introduced in our institute in December 2013 under the supervision of our Techniques and Medical Devices group (TaMDg), with strict audit and reporting requirements. In our unit, a team of clinicians, at a weekly multidisciplinary meeting, reviews images and clinical information of all patients with AAAs requiring treatment and recommends a suitable surgical or endovascular technique (including EVAS, where appropriate), according to the fitness of the patient, patient's preference, and anatomical features of the AAA. Informed consent was obtained for the procedure; this included an understanding that procedural outcomes would be evaluated and reported accordingly.

Pre-operative Plans

Surgeons use CT scans visualised with advanced software (Carestream Health Inc, Rochester, NY, USA) to obtain measurements for operative plans. The AAA is conventionally described in relation to of the proximal landing zone, the characteristics of the AAA sac, the distal zone and the vascular access. Figure 3.4 is a planning template commonly used for pre-operative endograft planning to evaluate morphological features of the AAA. Diameters are designated by 'D' and lengths by 'L'. Diameters are measured from outer-wall to outer-wall. The measurements include the most inferior diameter at the inferior renal artery (D1), the distal aortic neck at the start of the AAA (D2), the aortic bifurcation (D3), the largest AAA sac (maximum AAA diameter) (D4), and the common iliac arteries (D5 and D6). The lengths of the aortic neck (L1), the length from the lowest renal artery to the aortic bifurcation (L2) and the length of the AAA sac (L3). Also, the length of the distal landing zone is described as the distance from the aortic bifurcation to the common iliac artery bifurcation (L4 and L5). Minimal diameters should be recorded in the distal landing zone (D7 and D8) and external iliac artery access vessels. Neck angulation is the angle between the flow axis of the infrarenal neck and the body of the AAA.

Figure 3. 4 Diagram of the planning template showing the measurements needed for appropriate pre-operative endograft planning.[240]



Summary of dimeters and lengths measured for optimum AAA therapy, Diameters are designated by 'D' and lengths by 'L'. Diameters are measured from outer-wall to outer-wall.

Follow-up imaging protocol

Our follow-up protocol includes postoperative imaging by abdominal radiography on the first day; duplex ultrasound imaging and arterial-phase CT at 1 month; followed by yearly abdominal radiographs, duplex scans, and arterial-phase CT, except in patients with significant renal impairment and favourable 1-month CT appearances. CT data are reconstructed using the thinnest available slice (≤2 mm) before review.

Chapter 4: Methodology

4.1 Aims

The primary aim of this thesis was to examine the relationship between AAA growth post-EVAS, stent movement and different IFU groups. In detail, the aims of this study were:

1. Establish whether post EVAS AAA growth occurs
2. Assess the association between AAA growth and stent movement
3. Assess the relationship between AAA growth, stent movement and compliance with the anatomical criteria of the Nellix IFU

4.2 Null Hypotheses

The primary null hypothesis was that EVAS treated AAA growth.

The secondary null hypothesis was that AAA growth is not associated with stent movement and non-compliance with the anatomical criteria of the Nellix IFU.

4.3 Overview

This was a retrospective observational cohort study conducted at the Liverpool Vascular and Endovascular service (LiVES) between September 2017 and August 2018. Patients who underwent Endovascular AAA sealing were identified within the LIVES database and theatre records, and assessed against the inclusion criteria. A pro-forma was created and retrospective data collection was conducted using patient notes, an existing database and CT scans for aortic measurements. We used the STROBE checklist (Strengthening the reporting of observational studies in epidemiology) to present our observational study in this thesis (Appendix 8.1).[241]

4.4 Permissions and Ethical Approval

This project fell within a programme evaluating EVAS at our institution, therefore, formal ethical approval was not required; the study was registered as a service review (Service review number: AC04590)

4.5 Study population

The inclusion criteria were focused on EVAS performed on infra-renal AAA as an elective primary intervention. This excluded EVAS performed on ruptured AAAs, relining of previously inserted grafts, treatment of engraft failure and AAA in the juxta/suprarenal segments, in order to reduce heterogeneity.

The following eligibility criteria were applied:

Inclusion criteria:

1. Infra-renal EVAS
2. At least 2 postoperative CT scans: baseline at 1 month (≤6 weeks after device implantation) and 1 additional CT scan (minimum of 12 months from the initial implantation procedure)

Exclusion criteria:

1. Unavailable CT scans
2. Patients undergoing EVAS extending into the supra-renal segment (with chimneys)
3. Patients undergoing EVAS as a secondary intervention (after previous aortic AAA surgery)
4. Patients treated for ruptured AAAs

EVAS patients were identified on the departmental EVAS database which included demographics, clinical and procedural information.

4.6 Data collection

4.6.1. Baseline information

The EVAS database which was prospectively created by the LiVES team immediately following the procedure, was accessed and the inclusion criteria applied to select eligible patients and create a refined database. This database included information of patient demographics including age and sex; and comorbidities including ischemic heart disease (IHD), chronic respiratory disease, diabetes, renal impairment and cancer. We also included information about the current and previous smoking status of the patient. The American society of anaesthesiologist (ASA) grade was also noted along with whether the patient was on any of the following medications: antiplatelet therapy, statins or anticoagulants. (Appendix 8.2; Table 8.2)

4.6.2. Aortic anatomy

Pre-Operative plans performed by surgeons were used to collect this data, this included neck length, neck angulation, neck diameter, neck calcification/thrombus, shape of neck, preoperative maximum AAA diameter, maximum aortic lumen diameter, diameter at aortic bifurcation, maximum right common iliac artery (CIA) diameter, maximum left CIA diameter, Iliac tortuosity and maximum access diameter (Appendix 8.2; Table 8.3). The anatomical data enabled the determination of compliance to IFU-2013 and/or the newly refined IFU-2016.

4.6.3. Operative variables

All procedural variations were noted, including the implantation of an aorto-uni-iliac (AUI) device, using a single non-paired stent to seal the AAA. We also noted the type of anaesthesia used. Any unplanned events during surgery and additional procedures, planned or otherwise, were recorded. (Appendix 8.2; Table 8.4)

4.6.4. Thirty-day and follow-up outcomes

We noted Intra-operative complications, thirty-day postoperative outcomes and follow-up outcomes as listed in Appendix 8.2; Table 8.5. Intraoperative complications were categorised into device failure and operative complications. Device failures were directly linked to any defect, existing or arising during the procedure, in any part of the EVAS endoprosthesis including the console, endobag or stent.

For both the thirty-day outcomes and the follow-up outcomes we included information on re-intervention incidence and type. Death during the 30-day period and the follow-up period were noted and the cause specified.

4.6.5. CT Measurements

CT measurements can be divided into 3 groups: diameter measurements, volume measurements, and stent movement assessment The use of a Picture Archiving and Communications System (PACS) on the Carestream software (version 11.4.1.1011; Carestream Health Inc., Rochester, NY, USA) enabled the measurement of all these variables. The named author obtained all these measurements using the post-operative CT scans at baseline at one month and subsequent yearly scans. The exact time difference between EVAS and post-operative scans was recorded, in days. This dictated which year group the scan belonged to. (Appendix 8.2; Table 8.6)

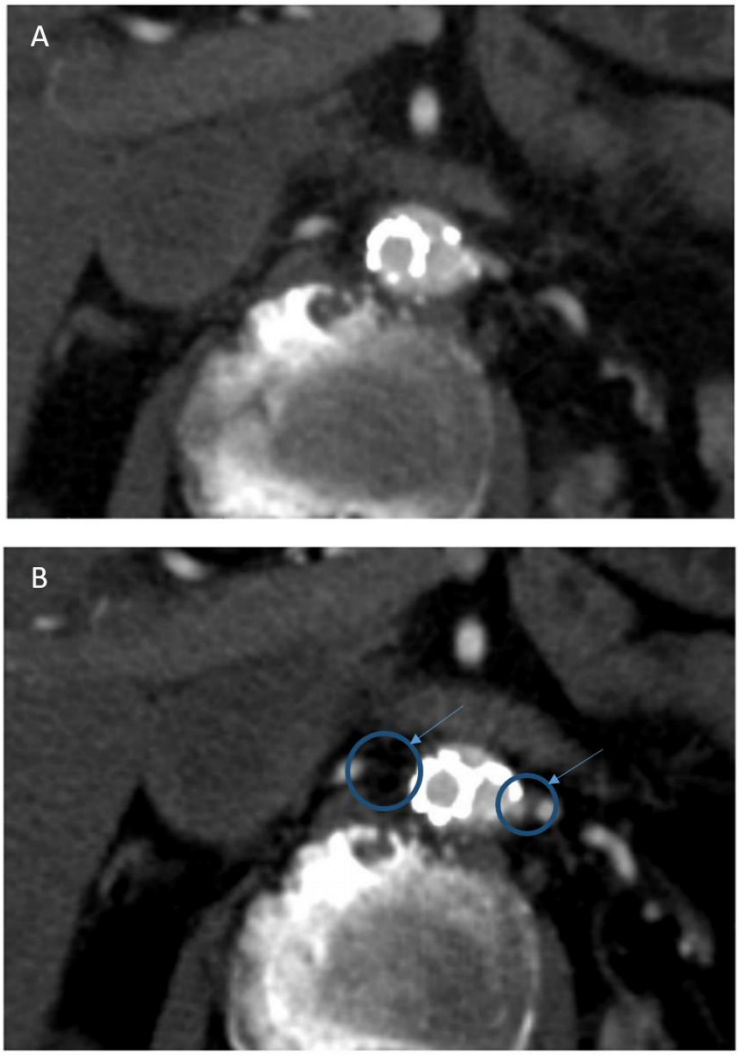
4.6.5.1 Diameter[199]

AAA diameter was measured as the maximum cross-section on reconstructed slices perpendicular to the main aortic axis from adventitia to adventitia. AAA growth was defined as a change of ≥5mm between the 1-month CT and subsequent scans, in accordance to the SVS definition.[242]

4.6.5.2 Volume measurements[243]

For volumes, the Carestream 'lesion livewire segmentation tool' was used to measure, at each slice (2 mm thickness obtained using the multiplanar reconstruction), the cross-sectional area of the AAA, starting below the point of the lowest renal artery to the aortic bifurcation. The lowest renal artery was identified by visualising a clear gap between the renal artery and the abdominal aortic stem (Figure 4.1). The aortic bifurcation was identified as one level (2mm slice) above the separation of the two common iliac arteries. Once the external outlines of both these slices was manually drawn, the software automatically generated a volume measurement of the accumulated outlines of all levels between these slices. Manual adjustments were performed after visual inspection of each cross-section, to eliminate imprecisions generated by inaccuracies of the software.[244] Volume measurements at one month post-EVAS was subtracted from those on follow-up scans to attain volume changes. Inter- and intra-observer variability was within 5% and therefore a change of more than 5% was deemed significant; this also a definition used by SVS.[242, 245] Inter-observer variability was assessed between the named author and two other reviewers.

Figure 4. 1 Volume measurements upper limit

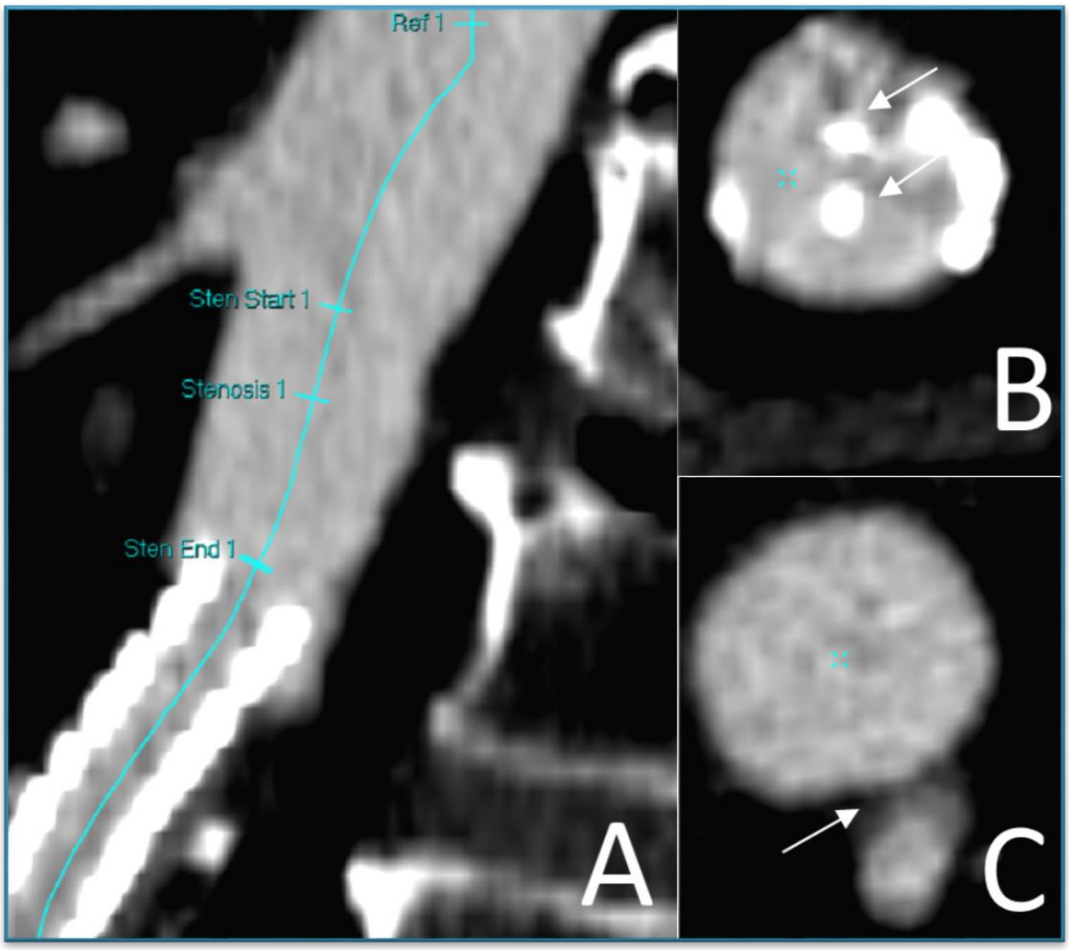


Two-dimensional oblique axial view of the abdomen, indicating the AA and the renal arteries emerging from it. (A) One slice above the limit of AA volume measurement (B) The point at which volume measurement should start. Arrows are pointing at the gap expected when identifying the level at which volume measurements should start.

4.6.5.3. Proximal displacement and migration[237]

The built-in 'vessel analysis' module of the Carestream software enabled the measurement of stent movement. Each scan was loaded onto a PACS workstation to generate a semi-automated central luminal line (CLL) through each stent using the 'Aorta Protocol' tool in the vessel analysis software. The 'Aorta Protocol' made switching from left stent to the right, and vice versa, automated and provided a more unified generation of the stent CLL. The CLL of each stent was checked by scrolling through all the anatomical planes available, ensuring that it was indeed traveling through the centre of the luminal space. Manual corrections were made, if necessary. A two-dimensional oblique axial view, perpendicular to the CLL, was used to determine the position of the stent graft against the specified reference vessel. We defined this as the most inferior point of the SMA, where a clear separation of this vessel from the aortic wall was visible, seen on the first oblique axial CLL reformatted image (Figure 4.2). The distance between this point and the first oblique axial CLL reformat that contained at least two stent struts was measured, reducing the probability of mistaking calcification for the actual stent graft. Each CLL measurement was compared with the same measurement on subsequent scans. Measurement differences between the CT scan at 1 month and subsequent scans at different points, for the same anatomic location, were used to determine whether device movement had occurred. Caudal movement was indicated by a positive value and cranial with a negative value. The bias (difference between true stent movement and the CT assessment), intra-observer and inter-observer variability when using this method for the proximal displacement definition had been previously reported.[246]

Figure 4. 2 Visual representation of the method of stent to SMA distance measurement.



Central luminal line (CLL) images (in blue) with corresponding oblique axial reformats demonstrate the technique used to record stent graft position against the superior mesenteric artery (A). (B) stent struts and corresponding to the perpendicular line to the CLL named 'Sten End 1'. (C) the inferior point of the SMA (clear gap from aorta), named on the CLL as 'Sten Start 1'.

Stent movement Definitions

The reporting standards of the SVS define device migration as movement of >10 mm relative to anatomical landmarks or any migration leading to symptoms or requiring therapy.[242] England et al specifically defined stent migration for the EVAS device in a recent study as ≥4mm relative to a vascular landmark.[246] This cut-off has also been used to define migration in fenestrated endovascular grafts.[247] Our method included assessing and reporting stent graft movement (≥4 mm), which we defined as proximal displacement in this thesis, and migration (>10mm), as defined by the SVS. Proximal displacement is stent movement in the caudal direction.

4.7. Data Analysis

SPSS version 22.0 (SPSS, Inc., Chicago, IL, USA) was used to analyse our data. Continuous variables were assessed for normality with the Kolmogorov–Smirnov test and presented as mean and standard deviation (SD) or median and range, according to the underlying distributions. Paired comparisons were performed with a t-test or Mann-Whitney U test, as appropriate. To assess agreement of AAA volume and maximum dimeter we correlated these using Pearson correlation. Kaplan-Meier survival curves were generated to visualise freedom from AAA growth, proximal displacement and migration patterns (separate figures for each these 'events'). When the standard error exceeded 10%, this was highlighted and a reference line added to the curve. The log rank test was used to compare AAA growth/proximal displacement/migration rates between different IFU groups. The Fisher's exact test was used to assess the association of AAA growth with stent movement.

A linear mixed model was used to analyse the trend and rate of AAA growth over time and associations of AAA growth with potential predictors. Shek et al published a stepwise method for the use of this model which we used in this thesis, as recommended by a senior statistician.[248]

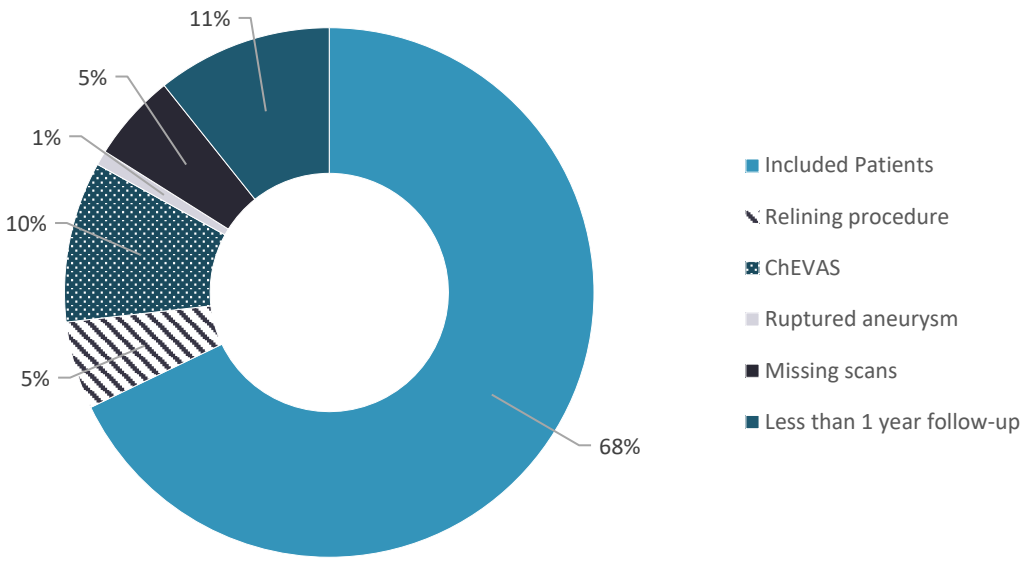
Chapter 5: Results

5.1. Patients

5.1.1. Selection

112 consecutive patients (86 men) with a mean (SD) age of 77 (7) years underwent EVAS between December 2013 and January 2018. The following patients were excluded: six who underwent EVAS to reline previously inserted grafts; eleven chimney-EVAS patients; one patient who underwent EVAS for a ruptured AAA; six who had missing post-operative scans due to loss to follow-up (2), death after 30 days but before 1 year (3) and severe renal impairment contra-indicating contrast CT (1) and twelve who had not yet had their 1-year post-operative scan. The patient with renal impairment was followed up using X-Ray imaging and displayed no stent movement. Figure 5.1 is a visual representation of the patient selection.

Figure 5. 1 Excluded patients with reasons



Abbreviations: ChEVAS, Chimney Endovascular aneurysm sealing.

5.1.2. Demographics and comorbidities

76 patients (58 men) were included in this study with a mean (SD) age of 76 (7.4) years. The patient population is one with multiple comorbidities including cancer and encompasses a large proportion of smokers. Over 70% of patients had an American Society of Anaesthesiologists (ASA) grade of 3 or more. Further details of demographics and comorbidities are displayed in Table 5.1.

Table 5. 1 Demographics, comorbidities and ASA grade of the patient cohort

Characteristics		**Number (%)**
Gender	Male	58 (76)
	Female	18 (24)
Ischemic heart disease		35 (46)
Respiratory disorders		26 (34)
Diabetes		11 (14)
Renal impairment		14 (18)
Hypertension		60 (79)
Cancer		8 (11)
Number of Comorbidities	0	6 (8)
	1	19 (25)
	2	26 (34)
	3	18 (24)
	4	6 (8)
	5	1 (1)
Smoking	Ex-smoker	36 (47)
	Current	22 (29)
ASA grade	2	22 (29)
	3	49 (64)
	4	5 (7)

Abbreviation ASA: American Society of Anaesthesiologists

5.1.3. Aorto-iliac anatomy

The anatomical features of 20 patients (26%) were within both IFU-2013 and IFU-2016; 56 (74%) patients were within IFU-2013; of these, 35 were outside the new IFU-2016 (46% of the whole population; 63% of the outside IFU-2016 population); 21 patients were outside both IFU-2013 and IFU-2016 (28% of the whole population; 38% of the outside IFU-2016 population). Please see visual representation on Figure 5.2. The proportion of patients that were compliant with IFU-2013 but were classed outside the revised IFU-2016 (35 patients) had at least one of the following anatomic features: 23 (66%) had a ratio of maximum AAA diameter to maximum aortic blood lumen diameter >1.4, 14 (40 %) had an aortic neck diameter >28 mm but <32 mm and 1 (3%) had a distal seal zone length <10 mm (Table 5.2). Pre-operative anatomical data is displayed in Table 5.3.

Table 5. 2 Reasons for non-compliance with IFU-2013 and IFU 2016

IFU-2013	**n (%)**	**IFU-2016**	**n (%)**
Iliac and femoral artery access that allows for atraumatic device introduction	0	No Change	-
Aortic proximal neck diameter range of 18 to 32mm	13 (17)	Aortic proximal neck diameter range of 18 to 28mm	27 (36)
Minimum aortic proximal neck length of ≥ 10mm	3 (4)	Criteria remains the same; however, the definition of aortic proximal neck length is updated to diameter change of 10% vs. previous 20%	3 (4)
Proximal aortic neck angulation of ≤60°	0	No Change	-
Aortic aneurysm with a blood lumen diameter of ≤60mm	2 (3)	Aortic aneurysm with a blood lumen diameter of ≤70mm	2 (3)
N/A	-	Ratio of maximum aortic aneurysm diameter to maximum aortic blood lumen diameter >1.4	23 (30)
Iliac arteries luminal diameter range of 9 to 35mm	5 (7)	Iliac artery blood lumen diameter range of 9 to 35mm outside the distal seal zone Distal seal zone: length of ≥ 10mm and diameter range of 9 to 25mm	6 (8)

Table 5. 3 AAA Characteristics according to instructions for use (IFU)

Anatomical feature	All patients	Patients outside IFU-2016	Outside IFU-2013
Aortic neck length (mm)	27 (6-65)	29(6-65)	23 (10-54)
Infra-renal neck angulation (degrees)	34 (0-78)	32 (0-77)	36 (0-70)
Maximum neck diameter (mm)	27 (5)	28(5)	28 (7)
Maximum aortic lumen diameter (mm)	44 (14)	41 (14)	42 (12)
Maximum AAA diameter (mm)	60 (54-93)	63(54-93)	61 (55-91)
Aortic bifurcation diameter (mm)	28 (14-54)	30(15-54)	29 (15-54)
Maximum right common iliac artery diameter (mm)	16 (4)	16(4)	16 (4)
Maximum left common iliac artery diameter (mm)	16 (4)	16(4)	16 (4)

Abbreviations: IFU, instructions for use; AAA, Abdominal aortic aneurysm;
Values are expressed as median (range) or mean (standard deviation).

5.1.4. Operative details

EVAS was performed using paired stents in all but three patients, who received an aorto-uni-iliac (AUI) device. Five patients received additional planned interventions during the EVAS procedure; one patient received two additional procedures. These included an ilio-femoral bypass, two femoral endartectomies, an iliac extension and one patient underwent both an ilio-femorial bypass and a femoral endartectomy. All but five patients received general anaesthesia; the remaining five received regional anaesthesia (sub-arachnoid or epidural). The surgeons followed the EVAS technique as described in 'Chapter 3: 3.6. EVAS in Liverpool'. To achieve proximal seal, surgeons routinely aimed to use the maximal length of neck available in each patient.

5.2. Procedural Outcomes

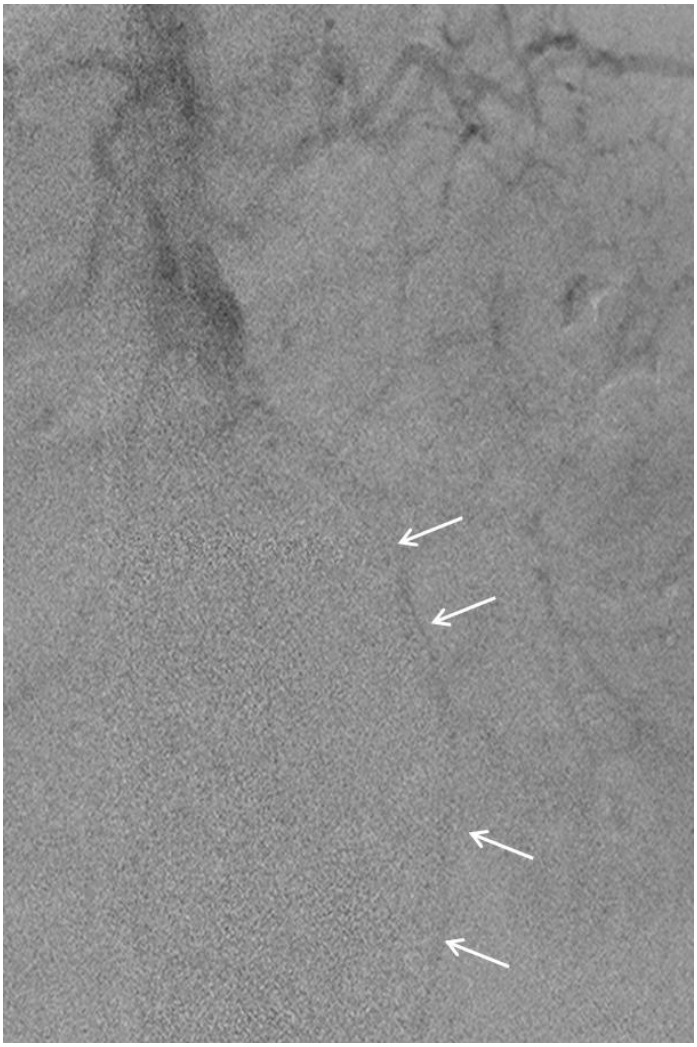
5.2.1. Intra-Operative outcomes

No deaths occurred intra-operatively. Five patients (7%) had intraoperative complications, two (3%) of which were due to device failure. The other complications were: one rupture of the distal external artery and two intraoperative AAA ruptures (asymptomatic, detected on the first follow-up CT). All non-device failure complications occurred in patients who were outside IFU-2016 but within IFU-2013.

The first device-failure was a rupture of the right stent balloon, which was successfully resolved by replacing the faulty catheter, as the stent had not been deployed and therefore could be taken out via the same deployment route with minimal femoral arterial damage. A new stent was then deployed into the AAA, with uneventful conclusion of the procedure. The anatomy of the AAA was outside IFU-2013 and IFU-2016. One year later, we found that this AAA had decreased in size (11% volume decrease; no significant diameter change) (Chapter 5.3) and the stents had not moved (Chapter 5.4).

The second device failure was a ruptured endobag. This was as the result of a defect of the Nellix pressure transducer which displayed an incorrect pressure. The stent was already unsheathed and it was not possible to retract it without causing damage to the vessels in its exit route. The surgeons considered conversion to open repair, however the fitness of the patient was of concern. They decided to seal the AAA with the remaining endobag. A small type Ia endoleak was detected at final angiography in the operating room (Figure 5.3). This was not visible on CT 48 hours after the procedure. This patient was within both IFU-2013 and IFU-2016. One year later, the AAA had grown significantly (6mm diameter increase and 9% volume increase) (Chapter 5.3) with evidence of proximal displacement/migration in both stents (left 6mm and right 12mm) (Chapter 5.4) but still no visible endoleak. The team considered re-intervention, however the patient has severe COPD precluding even further endovascular treatment.

Figure 5. 2 Visible type 1A endoleak detected on final angiography in the operating room.



Final completion angiogram using contrast shows evidence of a very small type 1a endoleak. Arrows are pointing towards blood flow outside and around the endobag.

5.2.2. Thirty-day outcomes

There were no post-operative deaths but 13 patients (17%) experienced a complication within 30-days of EVAS. Six of the complications were found in patients who were within IFU-2016; seven were in patients outside IFU-2016, three of which were within the original IFU-2013. Seven patients (9% of whole population; 54% of complicated population) required a secondary intervention. Three of the patients requiring re-interventions were within IFU-2016; and four were outside IFU-2016, none of which were within the original IFU-2013. The patient with the identified type 1a endoleak, which was as result of the previously described intra-operative complication, was within IFU-2013. Table 5.4 displays the 30-day morbidity and re-interventions.

Table 5. 4 Thirty-day outcomes

Variable	n.(%)	Details		
		Outside IFU-2016		Within IFU-2016 (n=20)
		Outside IFU-2013 and IFU-2016 (n=21)	Outside IFU-2016; within IFU-2013 (n=35)	
Complications	13 (17)	1 Limb ischemia 1 Access site haematoma 1 AKI 1 Paraparesis, acute coronary syndrome and neck of femur fracture	1 Limb ischemia 1 Left internal iliac coverage 1 Hospital acquired pneumonia	3 Limb ischemia 1 contrast nephropathy and AKI 1 Access site haematoma 1 Hospital acquired pneumonia
Re-intervention	7(9)	1 evacuation of haematoma 1 Insertion of spinal drain and hip hemiarthroplasty 1 Thrombectomy 1 Angioplasty + stenting	-	1 thrombectomy 1 femorofemoral bypass + fasciotomies 1 Embolectomy
Endoleak	1(1)	-	-	1 Type Ia, resolved within 48h
Death	0	-	-	-

Abbreviations: AKI, Acute Kidney Injury

5.2.3 Follow-up outcomes

Over a median follow-up of 24 months (range 12-48), a total of twelve patients underwent late re-interventions of whom nine were outside IFU-2016. One patient was also outside IFU-2013 (Re-interventions: 12% outside IFU-2016 vs 4% within IFU-2016). Three patients developed a type Ia endoleak: all were outside IFU-2016 with two also outside IFU-2013 (Endoleaks: 4% outside IFU-2016 vs 0% within IFU-2016). All patients with an endoleak displayed a significant change in AAA volume; two of which were AAA growth (11%, 5.3%, -11%; the latter however also displayed diameter increase of 10mm) (Chapter 5.3). All patients with an endoleak also had evidence of proximal displacement in at least one stent, with one patient also displaying migration (patient 1: right stent 6.4 mm; patient 2: left stent 5.1 mm; patient 3: left 13.4 mm and right 13.8 mm) (Chapter 5.4). Outcomes beyond 30 days included 8 deaths, none AAA related (Late deaths: 9% outside IFU-2016 vs 5% within IFU-2016). Re-interventions are summarised in Table 5.5.

Table 5. 5 Late Reinterventions

Follow-up range 12-48 months, median: 24 months

Variable	n.(%)	Details		
		Outside IFU-2016		Within IFU-2016 (n=20)
		Outside IFU-2013 and IFU-2016 (n=21)	Outside IFU-2016; within IFU-2013 (n=35)	
Re-intervention	12 (16)	1 External Iliac artery stent	1 tibial bypass 1 repeated EVAS 1 superficial femoral artery angioplasty 1 Limb extension 1 Nellix-in Nellix ChEVAS 1 Femoro-femoral bypass 2 Conversion to open repair	1 femoral thrombectomy and embolectomy 1 thrombectomy and Tibial bypass 1 Conversion to open repair
Endoleak	3 (4)	2 Type Ia	1 Type Ia	0
Death	8 (11)	3 Not aneurysm related*	4 Not aneurysm related*	4 Not aneurysm related*

ChEVAS: Chimney Endovascular aneurysm sealing: EVAS extending into the supra-renal segment using chimneys

*General Practitioners (GPs) were contacted to confirm the cause of death.

5.3 Aneurysm growth

5.3.1 Diameter Change

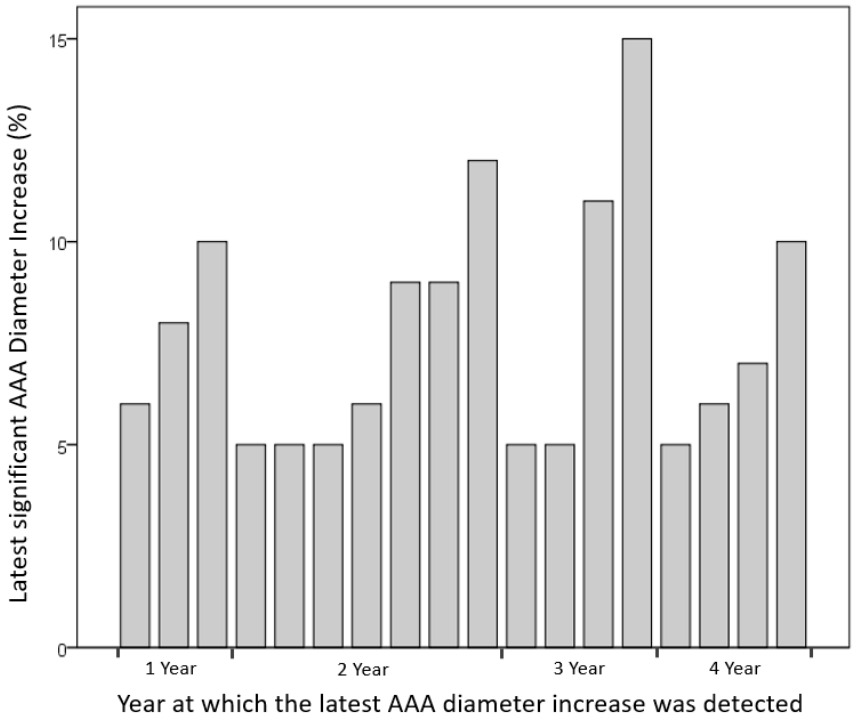
All patients had a one-month post EVAS CT scan; 75 patients had a CT scan at one year; forty-six patients had a 2-year post-EVAS CT; seventeen had a CT scan at 3-years; and seven had a CT at 4 years. Table 5.6 presents the extent and proportion of AAA growth, defined as an increase of ≥5mm in maximum AAA diameter over time. Just under a quarter of patients had AAA growth, detected at any time, by diameter change definition. The extent of significant diameter increase over time can be found on Figure 5.4. Figure 5.5 is of a survival plot of freedom from significant diameter increase over the 4 years.

Table 5. 6 Proportion and extent of AAA growth (diameter change) over time.

Time since procedure, years	Number of patients	AAA growth by diameter n.(%)	Median diameter change (mm) (Range)
1 year	75	5 (7)	6 (5-10)
2 year	46	11 (24)	5 (5-12)
3 year	17	4 (24)	8 (5-15)
4 year	7	4 (57)	6.5 (5-10)
At any time	76*	18 (24)	6 (5-15)

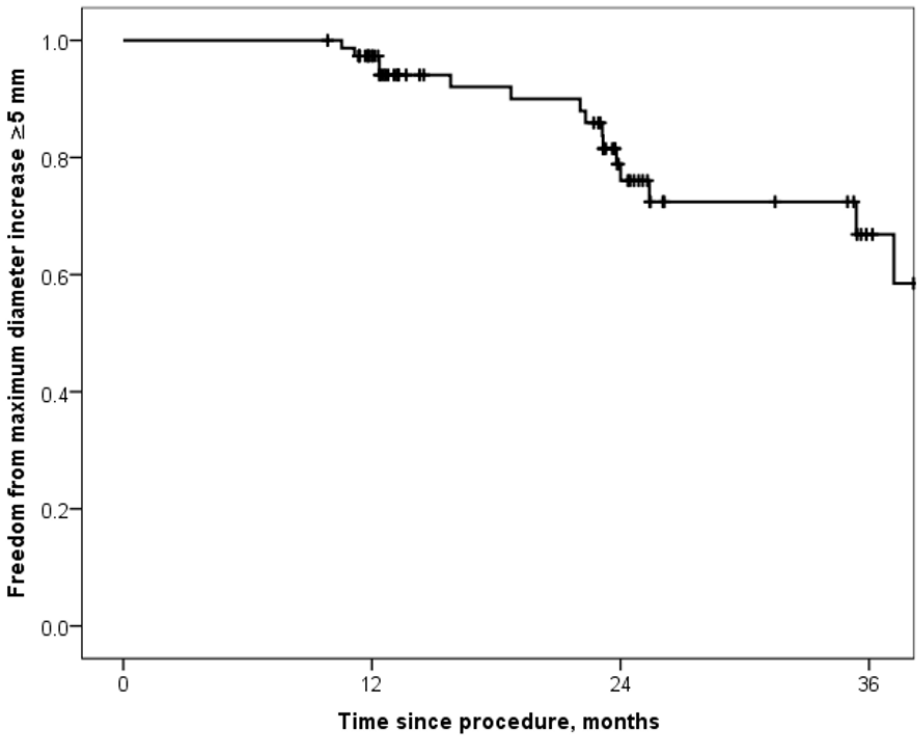
**note that one patient had their second scan 2 years after EVAS.*

Figure 5. 3 Maximum AAA diameter increase in patients with AAA growth by diameter and time of detection



Bars represent patients with AAA diameter increase of 5mm or more. Each bar represents the patient's latest maximum AAA diameter change. These are grouped into the different year groups according to when the latest diameter increase was noted.

Figure 5. 4 Freedom from AAA growth by diameter increase



Number at risk	76	75	46	17

Event: diameter increase of ≥5mm. *Survival table including standard errors over time can be found in appendix 8.3; Table 8.7. Standard errors of more than 10% were excluded from the graph.*

5.3.2. Absolute volume measurements

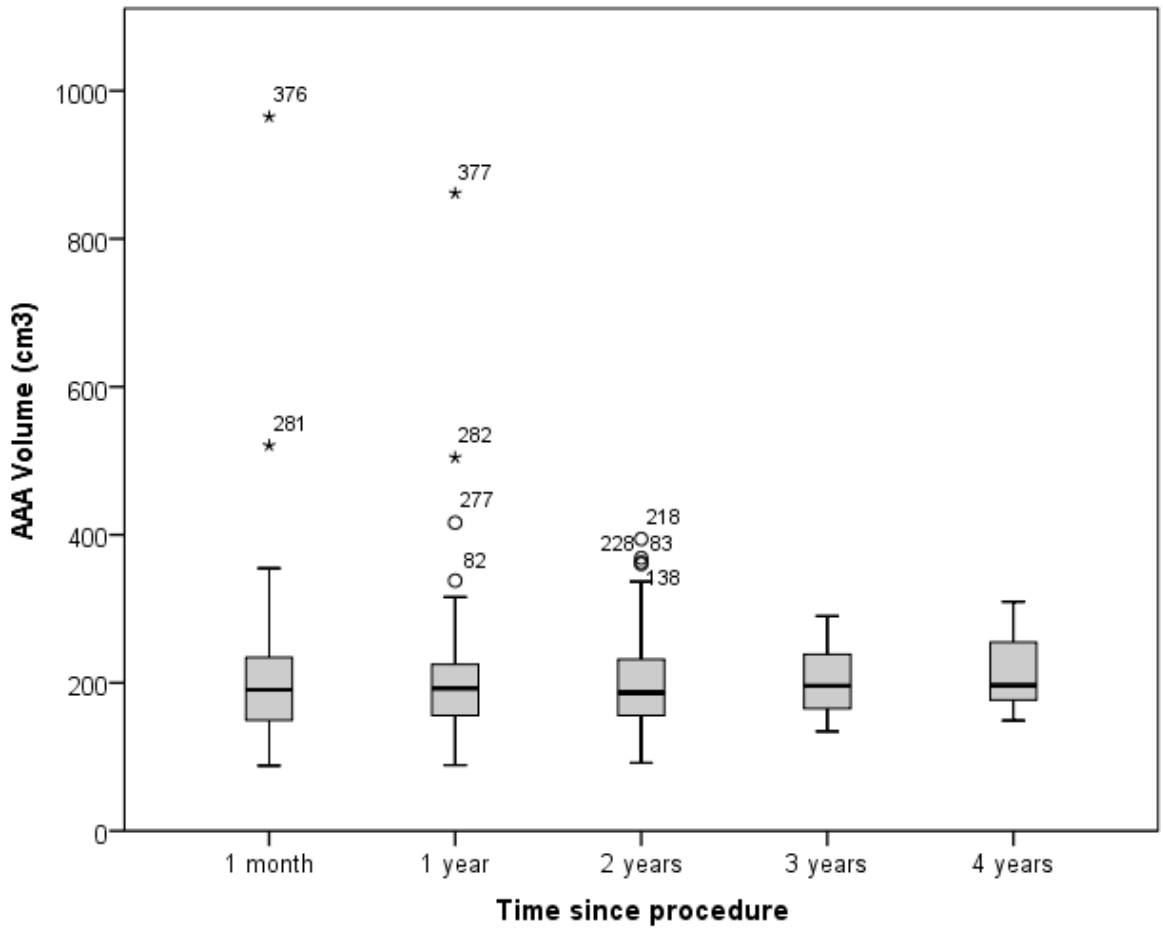
We were able to obtain AAA volume measurements for all available scans. Table 5.7 shows the median AAA volume measurements at each time point. Figure 5.6 shows the absolute volume measurements over time. We found 2 patients with statistically extreme volume measurements, who had been followed up for one year. We re-measured volumes of their AAAs and obtained similar results (less than 5% difference).

Table 5. 7 Absolute AAA volume over time

Time since procedure	Number of patients	Median absolute volume (cm^3) (Range)
1 month	76	191 (88 - 965)
1 year	75	192 (89 – 862)
2 year	46	187 (92 – 394)
3 year	17	196 (134 – 290)
4 year	7	197 (149 – 310)

One patient had their second scan at 2 years post-EVAS.

Figure 5. 5 Absolute volume measurements



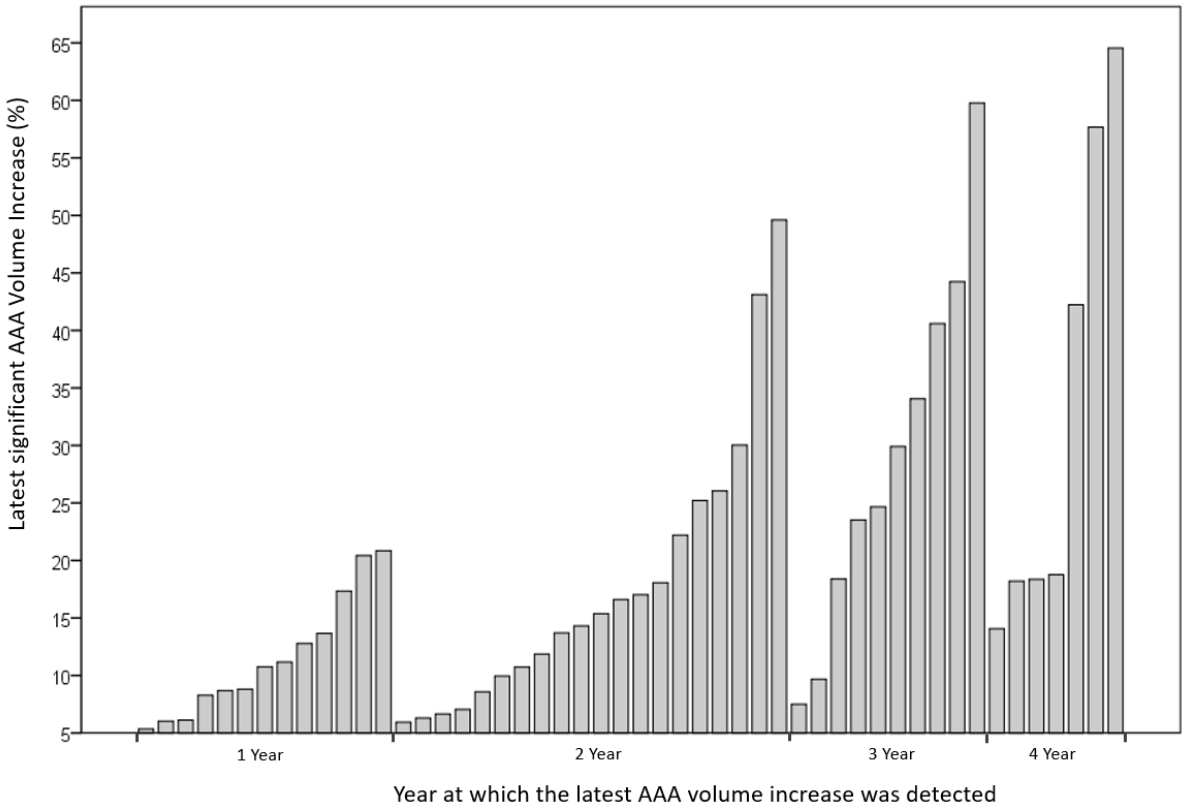
5.3.3. Volume Change

Table 5.8 presents the frequency of AAA growth of more than 5% at each post-operative time point. Just under one third of all AAAs demonstrated growth at one year; this proportion was more than double at 2 years and all but one AAA with a sufficiently long follow-up grew at years 3 and 4. The extent of AAA growth also appeared to increase over time (Figure 5.7). Figure 5.8 is of a survival plot of freedom from AAA growth over the 4 years. There were 5 patients, of patients with AAA growth, in whom the volume decreased in a subsequent scan. This was more than 5 % in only one patient (5.7%).

Table 5. 8 Proportion and extend of AAA growth (volume change) over time.

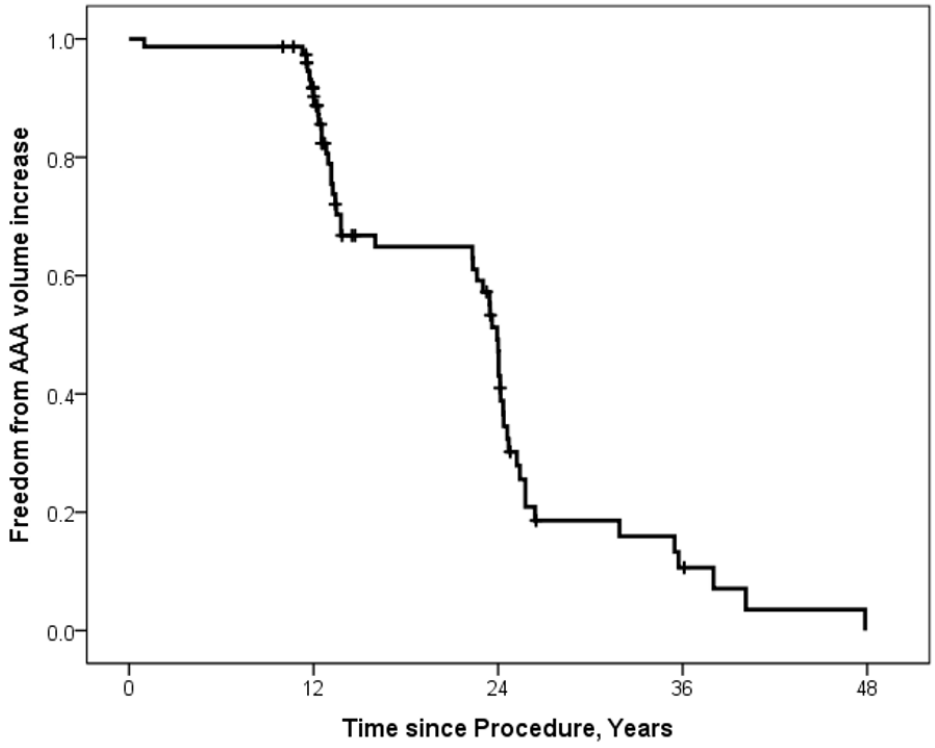
Time since procedure, years	Number of patients	Frequency of volume increase n.(%)	Median AAA growth (%) (Range)	Median absolute volume change (mm^3) (Range)
1 year	75	24 (32)	11 (5.3-21)	22 (16-62)
2 years	46	31 (67)	15 (6-50)	18 (9-29)
3 years	17	16 (94)	26 (8-60)	31 (11-80)
4 years	7	7 (100)	43 (18-65)	33 (24- 121)
At any time	76	50 (66)	14 (5.3-65)	25 (9 -121)

Figure 5. 6 Most recent AAA volume change in patients with AAA growth and time of detection



Bars represent patients with AAA volume increase of more than 5%. Each bar represents the patient's latest AAA volume change. These are grouped into the different year groups according to when the latest volume increase was noted.

Figure 5. 7 Freedom from AAA volume increase



Number at risk	76	75	46	17	7

Event: AAA volume increase of ≥5%. *Survival table including standard errors over time can be found in appendix 8.3; table 8.8.*

5.3.4. Diameter measurements vs volume measurements

We assessed the agreement of AAA volume and maximum dimeter and as expected all were significant at $p< 0.01$ (appendix 8.4; Table 8.17 and Figure 8.3). The R values of the comparison of diameters and volume measurements at one month, one year, two years, three years and four years were 0.701, 0.859, 0.761, 0.721 and 0.772 respectively. For 25 patient (33%) there was no AAA growth detected by either method; 17 (22%) AAA growth cases were detected by both methods; 33 (43%) were detected by volume measurements only and 1 (1%) was detected only by diameter measurements. For the rest of the thesis, we continue the analysis of AAA growth as detected by significant volume increase.

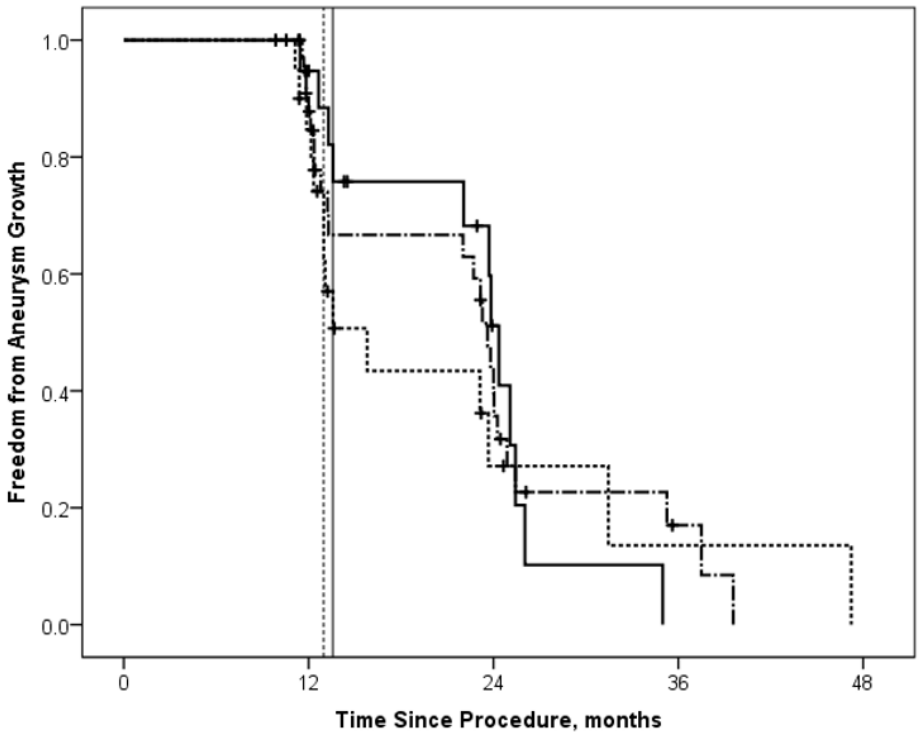
5.3.5. Aneurysm growth and IFU

Table 5.9 displays the distribution of AAA growth within different IFU groups. Figure 5.9 displays the freedom from AAA growth over time of the different IFU groups. Log rank test revealed no statistical difference between different IFU groups Figure 11.

Table 5. 9 AAA growth at any time in different IFU groups.

	AAA growth n./N(%)
IFU-2016 compliant	14/20 (70)
IFU-2016 non-compliant	36/56 (64)
IFU-2013 compliant (Non-compliant with IFU-2016)	24/35 (69)
Non-compliant with IFU-2013 and IFU-2016	12/21 (57)

Figure 5. 8 Freedom from AAA growth in different IFU groups.



Number at risk					
Non-compliant with IFU-2013 and IFU-2016	21	20	12	2	1
IFU-2013 compliant (Non-compliant with IFU-2016)	35	35	23	10	5
IFU-2016 compliant	20	20	11	5	1

Event: AAA volume increase of ≥5%. *IFU-2016 compliant: dotted line; IFU-2013 compliant (Non-compliant with IFU-2016): line and dot line; Non-compliant with IFU-2013 and IFU-2016: continuous line. Standard errors for each group at specified points can be found in appendix 8.3; Table 8.9. The reference lines specify the point at which the standard error exceeded 10% for a specific group; the pattern of the reference line corresponds to the group with the same pattern of the survival curve. The dotted reference line at 400 days: IFU-2016 compliant group. The continuous reference line at 419 days: Non-compliant with IFU-2013 and IFU-2016. Log Rank test results displayed no significant p values (appendix 8.3; Table 8.10).*

5.3.6. Patterns and causes of changes in volume

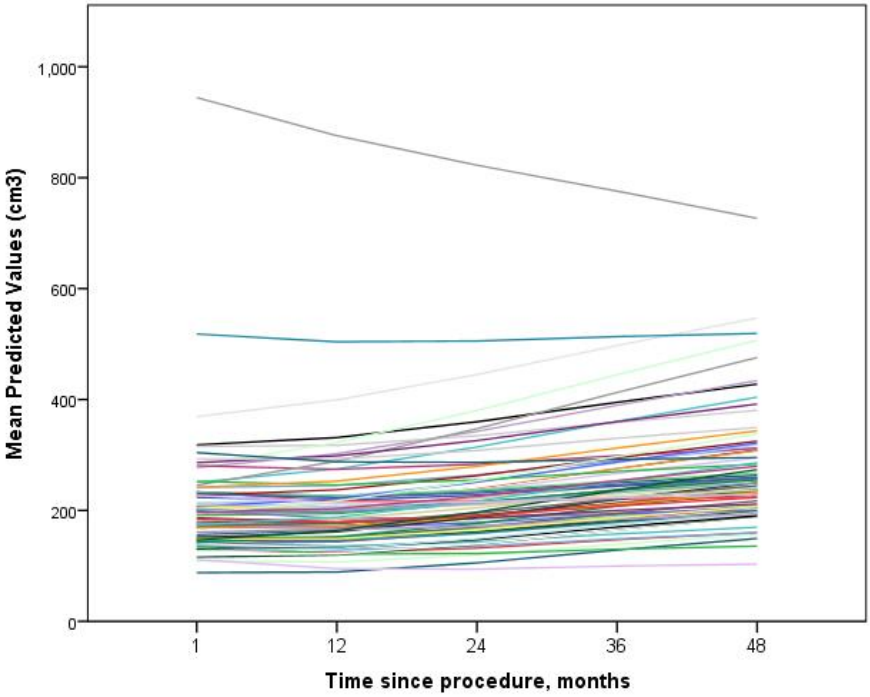
Extensive numerical data of the linear mixed model (LMM) results can be found in Appendix 8.5. Approximately 95% of the total variation in volume was due to inter-individual differences (appendix 8.5; step 1).

When assessing individual variation in AAA volume over time (appendix 8.5; step 2), time was statistically significant (p=0.000). This confirms that AAA volume changed over time. AAA mean estimated initial volume (at one month) was 196 cm^3 and this increased by 9.4 cm^3 per annum (p= 0.000). The correlation between the initial volume and the trajectories of growth were found to be significant with an overall negative estimate (β= -921.4; p=0.011). This suggests that smaller AAAs grew faster than larger ones.

We assessed whether the rate of AAA growth accelerated or decelerated over time (appendix 8.5; Step 3 and 4). Our results suggested that the initial increase was slow however it accelerated before slowing down again. (All relevant factors: $p<0.05$) (Figure 5.10).

Finally we applied potential predictors to the model to elicit any relevant associations (appendix 8.5; step 5). These included: age, neck angulation, neck length, neck diameter, ratio of maximum AAA diameter to maximum AAA lumen diameter, proximal displacement, migration. Neck diameter and migration were significantly associated with AAA volume growth (p=0.007 and p=0.036, respectively).

Figure 5. 9 Mean Predicted Values of all AAAs over time.



Results from the model with the best fit was applied: cubic growth curve model.

5.4. Stent movement

5.4.1. Absolute stent movement values

Over the 4-year period, forty-two patients had proximal displacement of ≥4mm in one or more stents. 25 were first detected within one year (33% of the point population of 75), 12 were detected at two-year follow-up (26% of the point population of 46) and a further six at 3-year follow-up (35% of the point population of 17).

Sixteen patients had migration of >10mm: five were first detected at one year (7% of point population of 75); seven at two years (15% of point population of 46); three at three years (18% of point population of 17) and one at 4 years (14% of point population of 7).

There were no differences in the incidence of proximal displacement/migration between the left and right stents (Table 5.10). Figure 5.11 shows the evolution of proximal displacement and migration over time. Figure 5.12 shows freedom from proximal displacement and migration.

Table 5. 10 Incidence and extent of proximal displacement and migration at any time.

	Total patient number	**Proximal displacement n(%)**	**Migration n(%)**	**Median proximal displacement (range)[a] (mm)**	**Median migration (range)[b] (mm)**
		≥4mm	**>10mm**	**≥4mm**	**>10mm**
Left stent	74	32(43)	10(14)	7.4(4-35)	16(12-35)
Right stent	75	35(47)	14(19)	8.2(4-28)	15(10.3-28)
Per patient	76	42(55)	16(21)	7.6(4-35)	15(10.3-35)

[a]among patients with proximal displacement, stent movement on most recent scan
[b]among patients with migration, stent movement on most recent scan

Figure 5. 10 Distance between stent and superior mesenteric artery in patients with migration (11a and 11b) and proximal displacement (11c and 11d) over time.

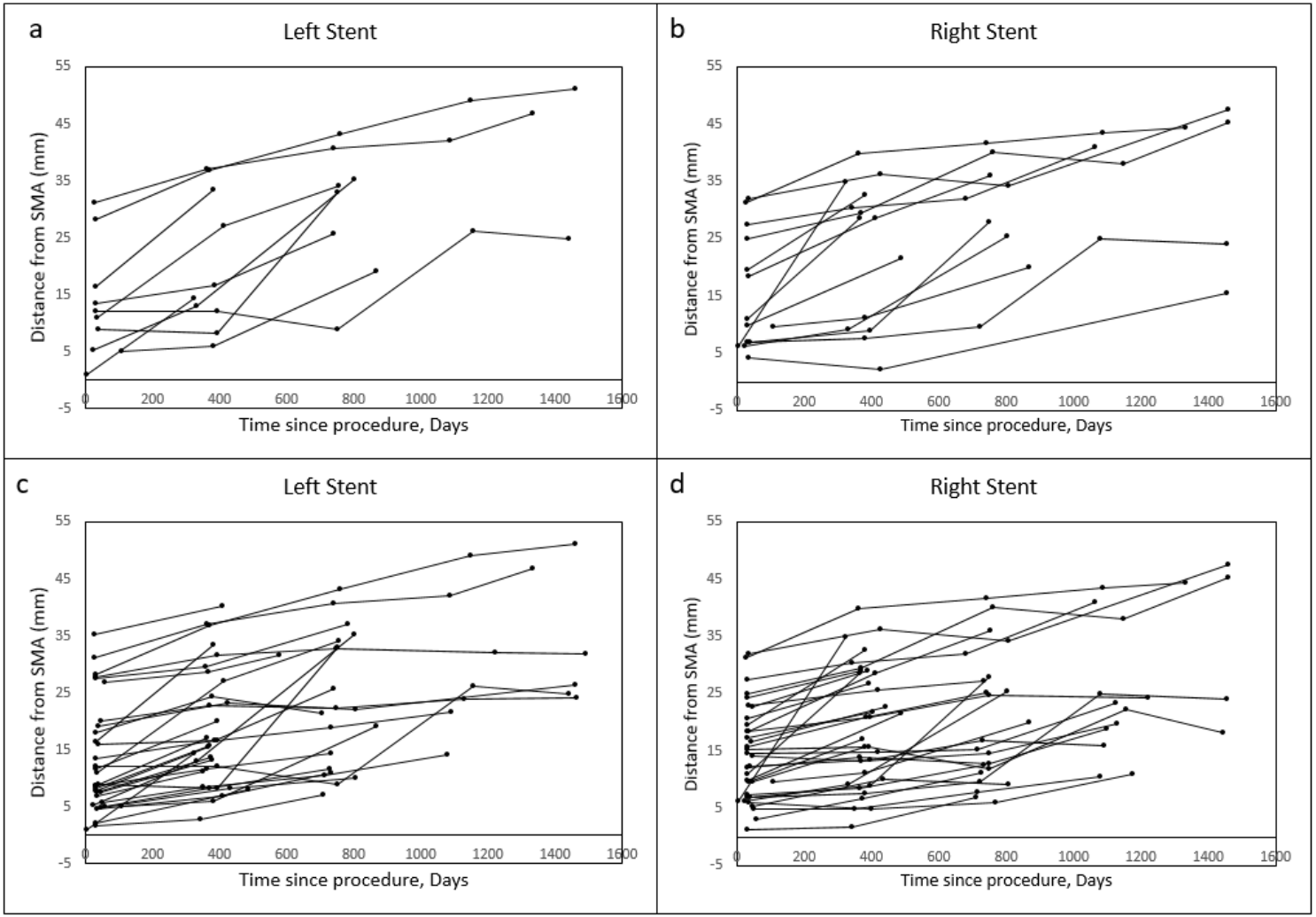


Figure 5. 11 Freedom from proximal displacement (11a) and migration (11b, 11c)

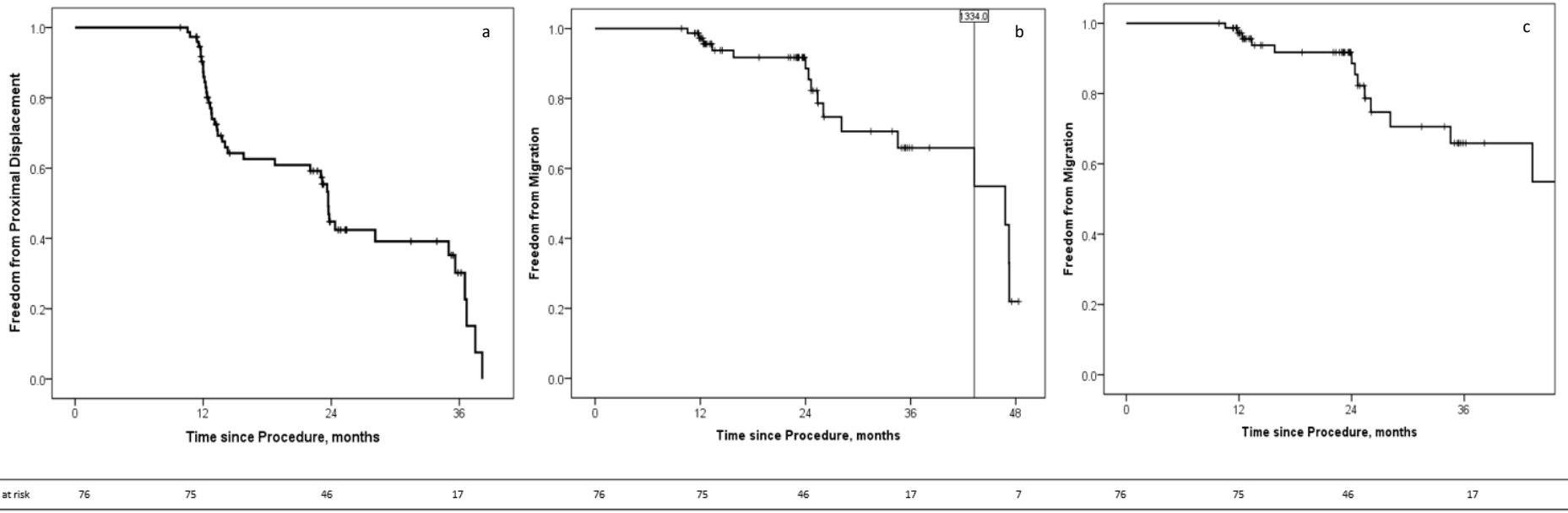


Figure 11a is of freedom from proximal displacement. Figure 11b is of the survival curve for migration including all data, the reference line set at 1334 days is the point at which the standard error has exceeded the 10% mark in one of the groups. 11c cuts off the data beyond 1334 days. Standard errors at specified points can be found in appendix 8.3; Table 8.11.

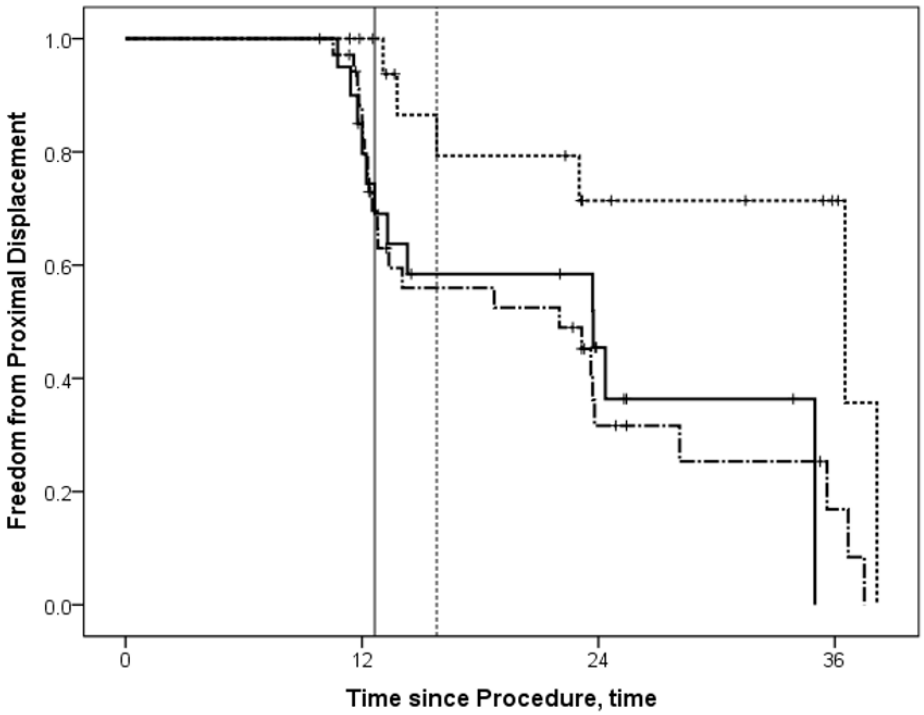
5.4.2. Stent movement and IFU

Proximal displacement/migration was affected by compliance with IFU-2013 and IFU-2016, as summarized in Table 5.11. The highest incidence of proximal displacement (66%) was observed when the device was outside both IFUs; this reduced to (30%) when the procedure was within the new IFU (IFU-2016). Figure 5.13 and 5.14 show freedom from proximal displacement and migration of each of the IFU groups. Proximal displacement was significantly more frequent among patients whose anatomy did not conform to any IFU (p=0.025).

Table 5. 11 Stent movement at any time in different IFU groups.

	Proximal displacement n./N (%)	**Migration n./N (%)**
IFU-2016 compliant	6/20 (30)	2/20 (10)
IFU-2016 non-compliant	36/56 (64)	14/56 (25)
IFU-2013 compliant (Non-compliant with IFU-2016)	22/35 (63)	9/35 (26)
Non-compliant with IFU-2013 and IFU-2016	14/21 (66)	5/21(24)

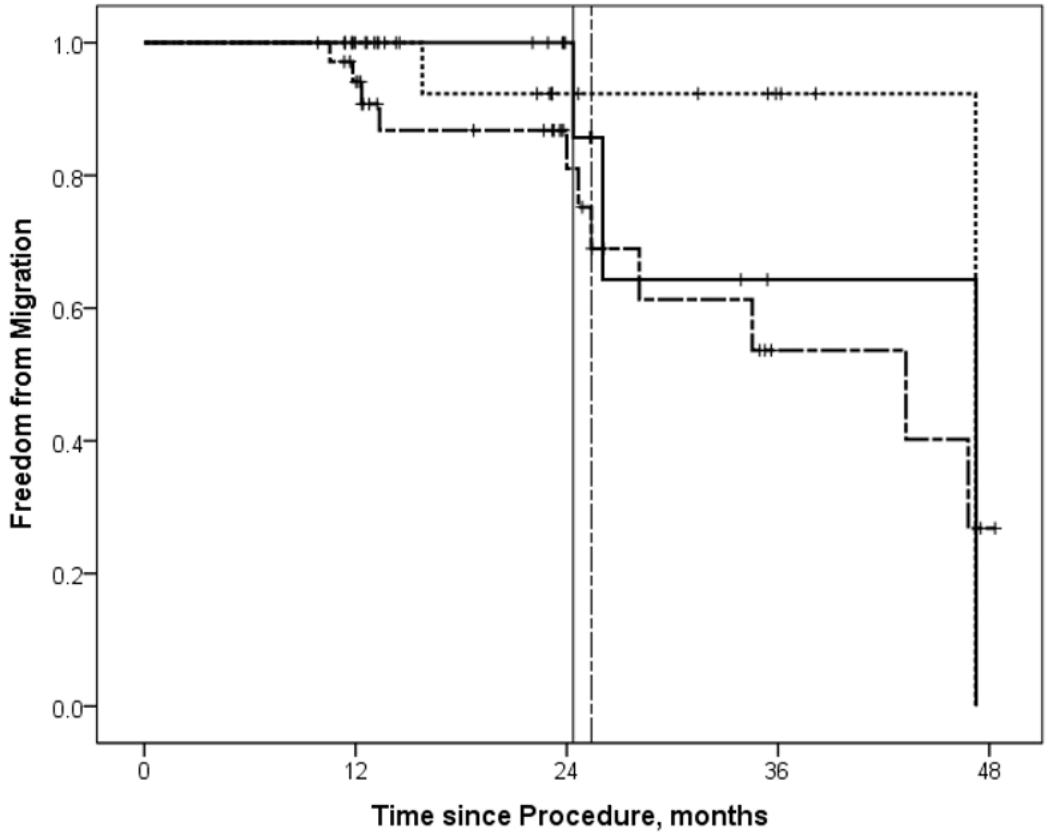
Figure 5. 12 Freedom from proximal displacement in IFU groups



Number at risk				
Non-compliant with IFU-2013 and IFU-2016	21	20	12	2
IFU-2013 compliant (Non-compliant with IFU-2016)	35	35	23	10
IFU-2016 compliant	20	20	11	5

Event: proximal displacement. IFU-2016 compliant: dotted line; IFU-2013 compliant (Non-compliant with IFU-2016): line and dot line; Non-compliant with IFU-2013 and IFU-2016: continuous line. Standard errors for each group at specified points can be found in appendix 8.3; Table 8.12. The reference lines specify the point at which the standard error exceeded 10% for a specific group; the pattern of the reference line corresponds to the group with the same pattern of the survival curve. The dotted reference line at 487 days: IFU-2016 compliant. The continuous reference line at 390 days: Non-compliant with IFU-2013 and IFU-2016. There was no statistically significant difference between curves (appendix 8.3; Table 8.13).

Figure 5. 13 Freedom from migration in IFU groups



Number at risk					
Non-compliant with IFU-2013 and IFU-2016	21	20	12	2	1
IFU-2013 compliant (Non-compliant with IFU-2016)	35	35	23	10	5
IFU-2016 compliant	20	20	11	5	1

Event: Migration. IFU-2016 compliant: dotted line; IFU-2013 compliant (Non-compliant with IFU-2016): line and dot line; Non-compliant with IFU-2013 and IFU-2016: continuous line. Standard errors for each group at specified points can be found in appendix 8.3; Table 8.14. The reference lines specify the point at which the standard error exceeded 10% for a specific group; the pattern of the reference line corresponds to the group with the same pattern of the survival curve. The line and dot reference line at 783 days: IFU-2013 compliant (Non-compliant with IFU-2016). The continuous reference line at 751 days: Non-compliant with IFU-2013 and IFU-2016. There was no statistically significant difference between curves (appendix 8.3; Table 8.15).

5.5. Aneurysm growth and Stent movement

Diameter increase was significantly associated with both migration and proximal displacement (p=0.000 and p=0.007, respectively). Significant volume increase was not associated with any stent movement (migration: p=0.236 and proximal displacement: 0.332).

In eight patients volume increase preceded proximal displacement; in five patients proximal displacement proceeded volume increase; in eighteen patients proximal displacement and volume increase were detected at the same time. Twenty patients only had volume increase and eleven only had proximal displacement. Fourteen patients displayed neither proximal displacement nor volume increase.

In four patients volume increase preceded migration; no patients displayed migration before volume increase; in nine patients migration and volume increase were detected at the same time. Thirty-eight patients only had volume increase and three only had migration. Twenty-two patients displayed neither migration nor volume increase.

In three patients diameter increase preceded proximal displacement; in seven patients proximal displacement preceded diameter increase; in five patients proximal displacement and diameter increase were detected at the same time. Three patients only had diameter increase and twenty-seven only had proximal displacement. Thirty-one patients displayed neither proximal displacement nor diameter increase.

In two patients diameter increase preceded migration; in one patients migration preceded diameter increase; in seven patients migration and diameter increase were detected at the same time. Eight patients only had diameter increase and six only had migration. Fifty-two patients displayed neither migration nor diameter increase.

Table 5. 12 Summary of the timing of AAA growth in relation to stent movement.

	Proximal displacement and Volume increase	Migration and Volume increase	Proximal displacement and diameter increase	Migration and diameter increase
AAA growth only	20	38	3	8
Stent movement only	11	3	27	6
AAA growth occurring first	8	4	3	2
Stent movement occurring first	5	0	7	1
AAA growth and stent movement occurring at the same time	18	9	5	7
Neither occurring	14	22	31	52

Chapter 6: Discussion

Summary of findings

Our primary hypothesis was that AAA growth continues after EVAS. This study confirms that AAA growth post-EVAS occurs in a significant proportion of patients. AAA growth is progressive, with smaller AAAs growing faster than larger ones. Our secondary hypothesis was that AAA growth is associated with stent movement and non-compliance with anatomical criteria of the Nellix IFU. We demonstrated that stent graft movement is frequent and is associated with anatomy outside the current IFU. Stent graft displacement can be progressive, can affect one or both stents and is associated with AAA growth, a finding that had not been previously described. We did not find an association between AAA growth and compliance with IFU.

Comparison with relevant literature

There is little data, in the literature, on AAA growth post-EVAS, which has not been widely reported using volume measurements. Zoethout et al reported the two-year outcomes of a multi-centre study based in the Netherlands.[249] They compared results of 168 patients who were within IFU-2013 to a subgroup of 48 patients who were also within IFU-2016 (22%); patients outside of IFU-2013 were not included in this study (96 patients). They reported AAA growth by diameter (SVS definition) in ten patients (6 %), two of which were within IFU-2016 (6 % vs 4.2 %).[249] Migration, which was defined as movement of 10 mm or more, occurred in 12 patients (7.1 %), none within IFU-2016 (7.1 % vs 0 %). They defined caudal movement as movement between 5 and 10 mm and this was observed in 25 patients (14.9 %), with four in the IFU-2016 group (14.9 % vs 8.3 %). This patient cohort was complicated by 9 late type I endoleaks (5.4 %) (one type Ib), of which 3 were in patients whose anatomy was IFU-2016 (5.4 % vs 6.3 %). Notwithstanding, the shorter length of follow-up, the incidence of endoleaks is similar to that in our study (5.4% vs 3.9%). However, AAA growth and stent movement were lower within this cohort. There are several factors that may have warranted this difference. First, the above study excluded the analysis of patients outside IFU-2013, whilst our

cohort included these. A further possible contributor to this differences may be discrepancies in measurement technique, as the above study did not describe this within their study. Additionally, only 26 patients within IFU-2016 had a follow-up of more than one year. The baseline CT scans were not performed at the same time in all patients, with 12% taking place after 6 months post-EVAS; further, only approximately 50% of patients underwent a CT scan at 2 years. Our study demonstrates that, when using the SVS definition for stent movement, detection is increasingly more frequent during follow-up (7% detection rate at one year, 15% at two years, 18% at three years and 14% at 4 years). Whilst AAA growth, by diameter definition, was detected in 7% of patients at one year but reached 24% at years two and three.

Migration and other types of stent displacement have also been described by other authors, although definition and measurement techniques have not been consistent in the literature. England et al previously reported, in a small cohort of our patients with shorter follow-up, the occurrence of post-EVAS stent migration, defined as and measured with the same criteria used in the present study as proximal displacement.[237] This study included 18 patients of which five displayed proximal displacement at one year follow-up in one or both stents (28%). Our study, which included the patient studied by England et al, detected proximal displacement in 33% of patients at one year (25 of 75 patients). Dorweiler et al described stent movement of ≥5mm occurring in 6 out of 24 patients at one year (25%).[250] However, Gossetti et al, in a multi-centre national registry, reported that only two out of 267 patients displayed stent movement of >4mm at one year (0.7%).[251] This study did not describe the method used to detect or measure movement. Only 67% of patients had a baseline CT/MRI scan, and it appears that other modalities, such as ultrasound scan, were used to obtain measurements. Van Veen et al reported stent movement of >5 mm in 6 out of 54 patients (11%) at one year post-EVAS in a study describing a new technique of capturing stent movement using 3-dimensional modalities on CT scans.[252] This study included a 'majority' of patients within IFU-2013, whilst in our study more than one-quarter were outside IFU-2013. It did not describe the number of patients in each of the IFU groups. Carpenter et al also reported migration (by SVS defintion) at one

year in three of 129 patients (2.3%) within IFU-2013. This migration was not associated with AAA growth (by SVS definition), endoleak or reintervention.[253] Description of measurement technique was also missing from this study.

In contrast, Van den Ham et al. did not observe stent movement at one year in 50 patients.[254] Although the authors stated that 38 patients were within IFU (76 %), it is unclear which IFU they were referring to. This study did not define the threshold of stent movement used. CT scans were assessed for anatomical changes and device stability. AAA volume was also measured and no difference was detected between overall post-EVAS scans. In our study we assessed AAA growth by volume using a different criteria with a set definition, it is, therefore difficult to compare the two studies.

Table 6. 1 AAA growth and stent movement within the current literature

Relevant study	Number of patients	AAA growth definition	AAA growth n. (%)	Stent movement definition	Stent movement n. (%)	Median Imaging Follow-up
Zoethout et al[255]	168	>5mm diameter change	10 (6)	≥10 mm Or ≥5 mm and requiring intervention	12 (7.1)	23 months
				5-10 mm	25 (15)	
England et al[237]	18	N/A	N/A	>4mm	5 (28)	12 months
Dorweiler et al[250]	24	Diameter change; Threshold unclear	1 (4.2) 7mm increase	≥5mm	6 (25)	12 months
Gossetti et al[256]	267	>5mm diameter change	2 (0.7)*	>4mm	2 (0.7)	12 months
Van Veen et al[257]	54	N/A	N/A	>5mm	6 (11)	12 months
Carpenter et al[253]	129	>5mm diameter change	2(1.6)	>10mm	3(2.3)	12 months
Van den Ham et al[254]	50	Volume; no set threshold	No overall growth	Threshold unclear	0 (0)	12 months

**It is unclear if the whole cohort was assessed, as the two patients with AAA enlargement were reported as an added point in endoleak results.*

We used two methods to report AAA growth. Volume measurements capture AAA growth over the whole AAA; this is important as the shape of the AAA may change and thrombus may grow away from the maximal cross-sectional area. In other words, a change of shape and volume may occur without significant changes in maximum diameter. This may be more likely post EVAS than post EVAR, as transmission of pressure from the landing zones may not occur uniformly in a sealed AAA. Volume measurements have been used to report changes in AAA post-EVAR using the same definition for change.[258] As EVAS is a relatively new technique, it may be appropriate to use the most sensitive method available to detect AAA growth. However, volume measurements, as described in this thesis, are cumbersome and time consuming, whereas automated methods are imprecise. Improvement in software would be necessary for volume measurement to be adopted more widely.

The incidence of migration and proximal displacement in our study should be interpreted in context, by comparing it to that observed post standard EVAR, when measured with similar criteria. A recent systematic review demonstrated a 6.3 % incidence of post-EVAR migration (≥5 mm) at 1-3 years; this was associated with poor anatomy and, unlike in our study, with type Ia endoleaks.[259]

Despite the occurrence of migration, proximal displacement and AAA growth in a substantial proportion of patients, we only observed three late endoleaks. It is generally thought that AAA growth rarely occurs in absence of AAA perfusion and pressurisation. It is also accepted that AAA pressurisation post-EVAS can occur in absence of a visible endoleak.[233] Considering the incidence of AAA growth observed in our study, we are concerned that this may be occurring in our patients. Our findings thus suggest that even small degrees of proximal displacement (≥4 mm) may be clinically significant. It is possible that small movements may allow blood to seep between the endobags and the aorta, or between the two endobags, effectively creating a wedge-like communication between the proximal circulation and the AAA. Even after thrombosis of such communication, AAA growth may occur, as thrombus is capable of transmitting pressure.[260] AAAs treated with EVAS may thus behave differently from those treated with EVAR during follow up.

In support of this thesis, our group recently highlighted the potential effect of certain forces (such as gravity and vibration) on implanted Nellix prostheses;[261] these forces would not be expected to have the same effect post-EVAR, due to the difference in mass between traditional endografts and the Nellix prosthesis. Whilst it is still unclear whether such effects have significant clinical consequences, their observation underlines that post-treatment evolution of AAAs treated by EVAS may be different from that of AAAs treated by EVAR.

Strengths and Limitations

This study has obvious limitations, as it was retrospective, limited to a single centre and to a relatively small population. Its strengths, however, include the prospective nature of clinical data collection, ensuring comprehensive capture of clinical adverse events, the low rate of loss to follow-up and the previously validated CT measurement techniques.

Whilst proximal stent displacement may be of particular relevance in short aortic necks, its clinical impact would also depend on the length of endobag/aorta apposition at the landing zones (the "seal"). In our experience, however, on CT scans, it is not always possible to measure length of seal, particularly in narrow necks, where the contour of endobags is difficult to define. We thus decided not to include this variable in this study, as we were not confident on our ability to measure it reliably. This is a potential weakness of this research, as we were not able to demonstrate adequate proximal seal in all patients post EVAS. It is now clear that it is difficult to utilise the proximal landing zone in full, when performing EVAS.[231] It is notable, however, that the surgeons performing EVAS in Liverpool always aimed to utilise all the available neck, when deploying the stents, thus any shortfall may be inherent to the very nature of the Nellix endoprosthesis, which is difficult to deploy precisely.

Further Considerations

We chose to use two definitions for stent movement, one being the SVS EVAR standard (>10 mm), which is more than 15 years old.[242] We believe that this definition, whilst established in the literature, may be outdated and inappropriate, partly because modern cross-sectional imaging allows the detection of much smaller stent movements, but also because of the inherent differences between EVAR and EVAS, which seals the AAA without active fixation at the landing zones (i.e. without radial force and/or hooks and barbs). As aortic necks are rarely perfectly cylindrical, even small post-EVAS stent movements may result in loss of contact between the endobags and the aorta (or between the two endobags), with consequent loss of seal and re-pressurization of the AAA. For these reasons, we also reported stent movement according to a less conservative (≥4 mm) definition previously used for fenestrated EVAR and EVAS.[237, 262] Interestingly, IFU 2016 compliant patients displayed approximately half the incidence of stent movement of the rest of the patients, regardless of definition (≥4 mm or >10 mm). As previously noted, there are many different measurement techniques and definition thresholds within the current literature, hence we believe that a new consensus is required on definitions in order to make meaningful comparisons between studies.

Whilst it is logical to assume that AAA growth follows stent movement, it is also theoretically possible that stent movement could be secondary to AAA growth, as such growth would create additional space for the stent/endobag complex to move into. In support of this theory, we observed AAA growth before stent movement in some cases. Unfortunately, our study cannot establish whether AAA growth was the cause or the consequence of stent movement. Further research is necessary to clarify this relationship.

Our findings confirm that there is a reduction in the incidence of stent movement when complying with IFU-2016, which was introduced after a higher than expected incidence of migration observed in American pre-marketing studies.[263] However, proximal displacement still occurred in almost one third of patients whose anatomy complied with IFU-2016. Our results should thus encourage clinicians to pursue close surveillance even in patients treated within IFU for early detection of stent

movement and AAA growth. They also support the notion that CT remains the cornerstone of post-EVAS follow-up imaging, despite the relatively high radiation exposure it entails. Other modalities, such as ultrasound scan (US), cannot produce reliable measurements of AAA volume or quantify stent graft displacement.

EVAS was readily embraced by the vascular community in 2013 with great optimism. The unfounded early belief that the sac-anchoring nature of the Nellix device would make stent movement impossible led clinicians to use EVAS on patients with poor anatomy and, in particular, very short necks.[226] Our results demonstrate that the device was indeed embraced too quickly and that the assumptions EVAS relies on are flawed. Our data also suggests that strict IFU compliance may only mask these flaws, rather than address them substantially. It is our opinion that active fixation at the landing zones may prevent some of the migration/displacement observed after EVAS and, possibly, reduce the incidence of AAA growth.

Our experience confirms that type II endoleaks post-EVAS are exceptionally rare. It is thus possible that changes in stent design that reduce or eliminate migration and proximal displacement may re-invigorate the enthusiasm for AAA sealing.

It is notable that, despite our findings on surveillance imaging, our clinical results are still acceptable, considering the treated population. Nevertheless, we do not think that clinicians should offer EVAS as a routine AAA treatment as long-term clinical data is still unavailable, and because our imaging findings appear progressive in nature. Further, our research was not designed to evaluate clinical outcome: larger comparative studies (with EVAR, open surgery or conservative management as comparators) would be required for this purpose.

It is debatable whether all patients treated by EVAS should be systematically recalled and informed of potential late post-EVAS complications. In view of our reassuring clinical results, and the fact that many of our patients are elderly and often unfit for further intervention, we have, so far, taken further action on a case-by-case basis.

Recommendations for Future Research

The present study was performed on a small sample size; this study on a larger multi-centre study sample with longer follow-up would provide the means of validating our finding and making robust associations. This would especially be useful when assessing the direction of the association between stent movement and aneurysm growth.

Assessment of endobag volume could facilitate the calculation of thrombus volume change over time and possibly explain the source of AAA growth (endobag volume subtracted from total AAA volume). Separation of the two endobags, which may be secondary to pressure within the AAA sac was not evaluated in our study, but has been described in the literature as an ominous sign.[264]

EVAS possess a unique appearance on CT imaging. Long term clinical studies matched to imaging findings are important to broaden the knowledge base and optimise complication predictions.

Our study suggests that diameter measurements are less sensitive than volume measurements, however, the method used in this study is time consuming and requires precise manual readjustments. Software developments to produce reliable automated volume measurements would be beneficial in assessing AAA growth post-EVAS in clinical practice.

Research and development of the present Nellix endoprosthesis with active fixation at landing zones may resolve the stent movement incidence. For this, mathematical modelling of a new adapted EVAS device would be needed, along with testing in engineering laboratory.

Large, multicentre comparative studies with EVAR would be useful to explore post-EVAS outcomes in context, and may provide a better understanding of the efficacy and cost effectiveness of EVAS.

Conclusion

Patients treated with EVAS are prone to AAA growth, irrespective of whether their aortic anatomy was IFU-compliant. Although post-EVAS endoleaks (as defined for EVAR) are rare, re-pressurisation of a sealed AAA may thus occur even when flow is not demonstrated within it. EVAS can also be complicated by stent movement, particularly when performed outside IFU. AAA growth is associated with stent movement, however it is unclear which is the cause and which is the effect. Clinicians should continue close surveillance post EVAS, particularly in patients treated outside IFU.

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Appendix

8.1. STROBE Statement

Table 8. 1 Checklist of items that should be included in reports of cohort studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions

		(*c*) Explain how missing data were addressed
		(*d*) If applicable, explain how loss to follow-up was addressed
		(*e*) Describe any sensitivity analyses
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) Summarise follow-up time (eg, average and total amount)
Outcome data	15*	Report numbers of outcome events or summary measures over time
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		

Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

8.2. Data collection

Table 8. 2 Variables Considered for Data Collection and Data Input

Category	Independent variable	Data Input
Demographic	Age	Years
	Sex	Male or Female
Comorbidities	Ischemic heart disease	Yes or No
	Reparatory chronic disorders	Yes or No
	Diabetes	Yes or No
	Renal Impairment	Yes or No
	Hypertension	Yes or No
	Cancer	Yes or No
	Smoking	Yes or No
	ASA Grade	Grade 1 to 5
Medications	Antiplatelet	Yes or No
	Statin	Yes or No
	Anticoagulants	Yes or No

Table 8. 3 Aortic anatomical variables considered for Data Collection and Data Input

Category	Independent variable	Data Input
Aortic Anatomical data	Neck length	Number
	Neck angulation	Number
	Neck diameter	Number
	Neck calcification/thrombus	Number
	Shape of neck	Number
	Maximum aortic lumen diameter	Number
	Diameter at aortic bifurcation	Number
	Maximum R CIA diameter	Number
	Maximum L CIA diameter	Number
	Diameter at R iliac bifurcation	Number
	Iliac tortuosity	Number
	Maximum access diameter	Number
	Maximum AAA diameter	Number
Instructions for use (IFU)	Within IFU-2013	Yes or No
	Within IFU-2016	Yes or No
	Reason outside IFU	Free-Text

Table 8. 4 Operative variables considered for Data Collection and Data Input

Category	Independent variable	Data input
Operative factors	Procedure	Free-Text
	Anaesthesia	General or local
	Intra-operative complication/events	Free-Text

Table 8. 5 Outcome variables considered for Data Collection and Data Input

Category	Independent variable	Data Input
30-day outcomes	Inpatient	Days
	ICU	Days
	Complication	Yes or No
	Complication type	Free-Text
	Re-Intervention	Yes or No
	Re-Intervention Type	Free-Text
	Endoleak	Yes or No
	Endoleak type	Free-Text
	Death	Yes or No
	Cause of Death	Free-Text
Follow-up Outcomes	Maximum Follow-up	Months
	Re-Intervention	Yes or No
	Re-intervention Type	Free-Text
	Endoleak	Yes or No
	Endoleak Type	Free-Text
	Death	Yes or No
	Cause of Death	Free-Text

Table 8. 6 Measurement variables considered for Data Collection and Data Input

Category	Independent variable	Data Input
Time of CT scan	One month	Days
	One year	Days
	Two years	Days
	Three years	Days
	Four years	Days
Volume measurements	One month AAA volume	Number
	One year AAA volume	Number
	Two years AAA volume	Number
	Three years AAA Volume	Number
Max diameter measurements	One month AP	Number
	One month Reconstructed	Number
	One Year AP	Number
	One year Reconstructed	Number
	Two years AP	Number
	Two years Reconstructed	Number
	Three years AP	Number
	Three years Reconstructed	Number
	Four years AP	Number
	Four years Reconstructed	Number
Stent movement data	Left: Distance at one month	Number
	Right: Distance at one month	Number
	Left: Distance at one year*	Number
	Right: Distance at one year*	Number
	Left: Distance change one month to one year*	Number
	Right: Distance change one month to one year*	Number
	Left: stent movement at one year*	Yes or No
	Right: stent movement at one year*	Yes or No

*same independent variables for two year CT scan, three year CT scan and four year CT scan

8.3. Kaplan-Meier curves survival tables

Table 8. 7 Survival Table of freedom from AAA maximum diameter increase

Survival Table

	Time	Status	Cumulative Proportion Surviving at the Time		N of Cumulative Events	N of Remaining Cases
			Estimate	Std. Error		
1	304.000	.00	.	.	0	75
2	325.000	1.00	.987	.013	1	74
3	344.000	1.00	.973	.019	2	73
4	350.000	.00	.	.	2	72
5	351.000	.00	.	.	2	71
6	351.000	.00	.	.	2	70
7	352.000	.00	.	.	2	69
8	360.000	.00	.	.	2	68
9	363.000	.00	.	.	2	67
10	364.000	.00	.	.	2	66
11	365.000	.00	.	.	2	65
12	366.000	.00	.	.	2	64
13	370.000	.00	.	.	2	63
14	371.000	.00	.	.	2	62
15	374.000	.00	.	.	2	61
16	379.000	.00	.	.	2	60
17	381.000	1.00	.	.	3	59
18	381.000	1.00	.941	.029	4	58
19	381.000	.00	.	.	4	57
20	383.000	.00	.	.	4	56
21	387.000	.00	.	.	4	55
22	390.000	.00	.	.	4	54
23	394.000	.00	.	.	4	53
24	403.000	.00	.	.	4	52
25	408.000	.00	.	.	4	51
26	408.000	.00	.	.	4	50
27	410.000	.00	.	.	4	49
28	421.000	.00	.	.	4	48
29	441.000	.00	.	.	4	47
30	447.000	.00	.	.	4	46
31	487.000	1.00	.920	.035	5	45
32	577.000	1.00	.900	.040	6	44
33	680.000	1.00	.880	.044	7	43
34	688.000	1.00	.859	.047	8	42

35	700.000	.00	.	.	8	41
36	707.000	.00	.	.	8	40
37	710.000	.00	.	.	8	39
38	713.000	1.00	.837	.051	9	38
39	714.000	1.00	.815	.054	10	37
40	714.000	.00	.	.	10	36
41	715.000	.00	.	.	10	35
42	718.000	.00	.	.	10	34
43	728.000	.00	.	.	10	33
44	731.000	.00	.	.	10	32
45	732.000	.00	.	.	10	31
46	734.000	1.00	.789	.058	11	30
47	735.000	.00	.	.	11	29
48	737.000	.00	.	.	11	28
49	740.000	1.00	.761	.063	12	27
50	751.000	.00	.	.	12	26
51	754.000	.00	.	.	12	25
52	760.000	.00	.	.	12	24
53	767.000	.00	.	.	12	23
54	773.000	.00	.	.	12	22
55	780.000	.00	.	.	12	21
56	783.000	1.00	.724	.069	13	20
57	784.000	.00	.	.	13	19
58	784.000	.00	.	.	13	18
59	803.000	.00	.	.	13	17
60	805.000	.00	.	.	13	16
61	970.000	.00	.	.	13	15
62	1078.000	.00	.	.	13	14
63	1087.000	.00	.	.	13	13
64	1091.000	1.00	.669	.083	14	12
65	1092.000	.00	.	.	14	11
66	1098.000	.00	.	.	14	10
67	1106.000	.00	.	.	14	9
68	1115.000	.00	.	.	14	8
69	1147.000	1.00	.585	.107	15	7
70	1176.000	.00	.	.	15	6
71	1334.000	1.00	.488	.126	16	5
72	1443.000	.00	.	.	16	4
73	1456.000	1.00	.366	.142	17	3
74	1457.000	.00	.	.	17	2

75	1465.000	1.00	.183	.147	18	1
76	1490.000	.00	.	.	18	0

Table 8. 8 Survival Table of freedom from AAA volume increase

Survival Table

	Time	Status	Cumulative Proportion Surviving at the Time		N of Cumulative Events	N of Remaining Cases
			Estimate	Std. Error		
1	30.000	1.00	.987	.013	1	75
2	304.000	.00	.	.	1	74
3	325.000	.00	.	.	1	73
4	343.000	1.00	.973	.019	2	72
5	350.000	.00	.	.	2	71
6	351.000	1.00	.960	.023	3	70
7	351.000	.00	.	.	3	69
8	352.000	.00	.	.	3	68
9	353.000	1.00	.946	.027	4	67
10	357.000	1.00	.931	.030	5	66
11	360.000	1.00	.917	.032	6	65
12	363.000	.00	.	.	6	64
13	364.000	.00	.	.	6	63
14	364.000	.00	.	.	6	62
15	365.000	1.00	.902	.035	7	61
16	365.000	.00	.	.	7	60
17	366.000	1.00	.887	.038	8	59
18	370.000	.00	.	.	8	58
19	371.000	.00	.	.	8	57
20	372.000	.00	.	.	8	56
21	374.000	1.00	.872	.040	9	55
22	375.000	1.00	.856	.042	10	54
23	379.000	.00	.	.	10	53
24	381.000	1.00	.	.	11	52
25	381.000	1.00	.823	.047	12	51
26	381.000	.00	.	.	12	50
27	383.000	.00	.	.	12	49
28	387.000	.00	.	.	12	48
29	390.000	1.00	.806	.049	13	47
30	394.000	1.00	.789	.051	14	46
31	400.000	1.00	.	.	15	45
32	400.000	1.00	.755	.054	16	44
33	403.000	1.00	.738	.055	17	43
34	408.000	1.00	.721	.057	18	42

35	408.000	.00	.	.	18	41
36	410.000	1.00	.703	.058	19	40
37	419.000	1.00	.	.	20	39
38	419.000	1.00	.668	.060	21	38
39	421.000	.00	.	.	21	37
40	441.000	.00	.	.	21	36
41	447.000	.00	.	.	21	35
42	487.000	1.00	.649	.061	22	34
43	679.000	1.00	.630	.062	23	33
44	680.000	1.00	.611	.063	24	32
45	688.000	1.00	.591	.064	25	31
46	700.000	1.00	.572	.065	26	30
47	707.000	.00	.	.	26	29
48	713.000	1.00	.553	.066	27	28
49	714.000	1.00	.533	.066	28	27
50	715.000	.00	.	.	28	26
51	718.000	1.00	.512	.067	29	25
52	728.000	1.00	.492	.067	30	24
53	730.000	1.00	.471	.067	31	23
54	731.000	1.00	.	.	32	22
55	731.000	1.00	.430	.067	33	21
56	734.000	1.00	.410	.067	34	20
57	734.000	.00	.	.	34	19
58	735.000	1.00	.388	.067	35	18
59	740.000	1.00	.367	.067	36	17
60	741.000	1.00	.345	.066	37	16
61	748.000	1.00	.324	.066	38	15
62	751.000	1.00	.302	.065	39	14
63	754.000	.00	.	.	39	13
64	767.000	1.00	.279	.064	40	12
65	773.000	1.00	.256	.062	41	11
66	784.000	1.00	.	.	42	10
67	784.000	1.00	.209	.059	43	9
68	803.000	1.00	.186	.057	44	8
69	805.000	.00	.	.	44	7
70	970.000	1.00	.159	.055	45	6
71	1079.000	1.00	.133	.052	46	5
72	1087.000	1.00	.106	.048	47	4
73	1098.000	.00	.	.	47	3
74	1156.000	1.00	.071	.043	48	2

75	1220.000	1.00	.035	.033	49	1
76	1456.000	1.00	.000	.000	50	0

Table 8. 9 Survival Table of freedom from AAA volume increase in different IFU groups

IFU groups: (1) *IFU-2016 compliant; (2) IFU-2013 compliant (Non-compliant with IFU-2016); (3) Non-compliant with IFU-2013 and IFU-2016.*

Survival Table

IFUGroups		Time	Status	Cumulative Proportion Surviving at the Time		N of Cumulative Events	N of Remaining Cases
				Estimate	Std. Error		
1.00	1	343.000	1.00	.950	.049	1	19
	2	351.000	1.00	.900	.067	2	18
	3	351.000	.00	.	.	2	17
	4	366.000	1.00	.847	.081	3	16
	5	375.000	1.00	.794	.092	4	15
	6	380.000	1.00	.741	.100	5	14
	7	387.000	.00	.	.	5	13
	8	400.000	1.00	.	.	6	12
	9	400.000	1.00	.627	.112	7	11
	10	403.000	1.00	.570	.116	8	10
	11	408.000	.00	.	.	8	9
	12	419.000	1.00	.507	.119	9	8
	13	421.000	.00	.	.	9	7
	14	487.000	1.00	.434	.122	10	6
	15	713.000	1.00	.362	.121	11	5
	16	715.000	.00	.	.	11	4
	17	730.000	1.00	.271	.120	12	3
	18	760.000	.00	.	.	12	2
	19	970.000	1.00	.136	.113	13	1
	20	1456.000	1.00	.000	.000	14	0
2.00	1	325.000	.00	.	.	0	34
	2	350.000	.00	.	.	0	33
	3	357.000	1.00	.970	.030	1	32
	4	360.000	1.00	.939	.042	2	31
	5	365.000	1.00	.909	.050	3	30
	6	365.000	.00	.	.	3	29
	7	370.000	1.00	.878	.057	4	28
	8	371.000	.00	.	.	4	27
	9	374.000	1.00	.845	.064	5	26
	10	379.000	.00	.	.	5	25
	11	381.000	1.00	.	.	6	24
	12	381.000	1.00	.778	.074	7	23
	13	381.000	.00	.	.	7	22

	14	383.000	.00	.	.	7	21
	15	394.000	1.00	.741	.080	8	20
	16	408.000	1.00	.704	.084	9	19
	17	410.000	1.00	.667	.087	10	18
	18	679.000	1.00	.629	.090	11	17
	19	700.000	1.00	.592	.092	12	16
	20	714.000	1.00	.555	.093	13	15
	21	714.000	.00	.	.	13	14
	22	718.000	1.00	.516	.095	14	13
	23	728.000	1.00	.476	.095	15	12
	24	734.000	1.00	.436	.095	16	11
	25	740.000	1.00	.397	.095	17	10
	26	741.000	1.00	.357	.093	18	9
	27	748.000	1.00	.317	.091	19	8
	28	754.000	.00	.	.	19	7
	29	767.000	1.00	.272	.088	20	6
	30	784.000	1.00	.227	.085	21	5
	31	805.000	.00	.	.	21	4
	32	1087.000	1.00	.170	.080	22	3
	33	1098.000	.00	.	.	22	2
	34	1156.000	1.00	.085	.072	23	1
	35	1220.000	1.00	.000	.000	24	0
3.00	1	304.000	.00	.	.	0	20
	2	352.000	.00	.	.	0	19
	3	353.000	1.00	.947	.051	1	18
	4	363.000	.00	.	.	1	17
	5	364.000	.00	.	.	1	16
	6	370.000	.00	.	.	1	15
	7	390.000	1.00	.884	.078	2	14
	8	410.000	1.00	.821	.094	3	13
	9	419.000	1.00	.758	.106	4	12
	10	441.000	.00	.	.	4	11
	11	447.000	.00	.	.	4	10
	12	680.000	1.00	.682	.120	5	9
	13	707.000	.00	.	.	5	8
	14	731.000	1.00	.597	.132	6	7
	15	735.000	1.00	.512	.138	7	6
	16	737.000	.00	.	.	7	5
	17	751.000	1.00	.409	.143	8	4
	18	773.000	1.00	.307	.139	9	3

	19	784.000	1.00	.205	.125	10	2
	20	803.000	1.00	.102	.096	11	1
	21	1079.000	1.00	.000	.000	12	0

Table 8. 10 Log rank results of AAA volume increase in different IFU groups

Log Rank (Mantel – Cox)	IFU-2016 Compliant		IFU-2013 compliant (Non-compliant with IFU-2016)		*Non-compliant with IFU-2013 and IFU-2016*	
	X^2	P value	X^2	P value	X^2	P value
IFU-2016 Compliant			0.251	0.616	0.698	0.404
IFU-2013 compliant (Non-compliant with IFU-2016)	0.251	0.616			0.000	0.997
Non-compliant with IFU-2013 and IFU-2016	0.698	0.404	0.000	0.997		

Figure 8. 1 Freedom from AAA growth in different IFU groups (Cut off at SE>10%)

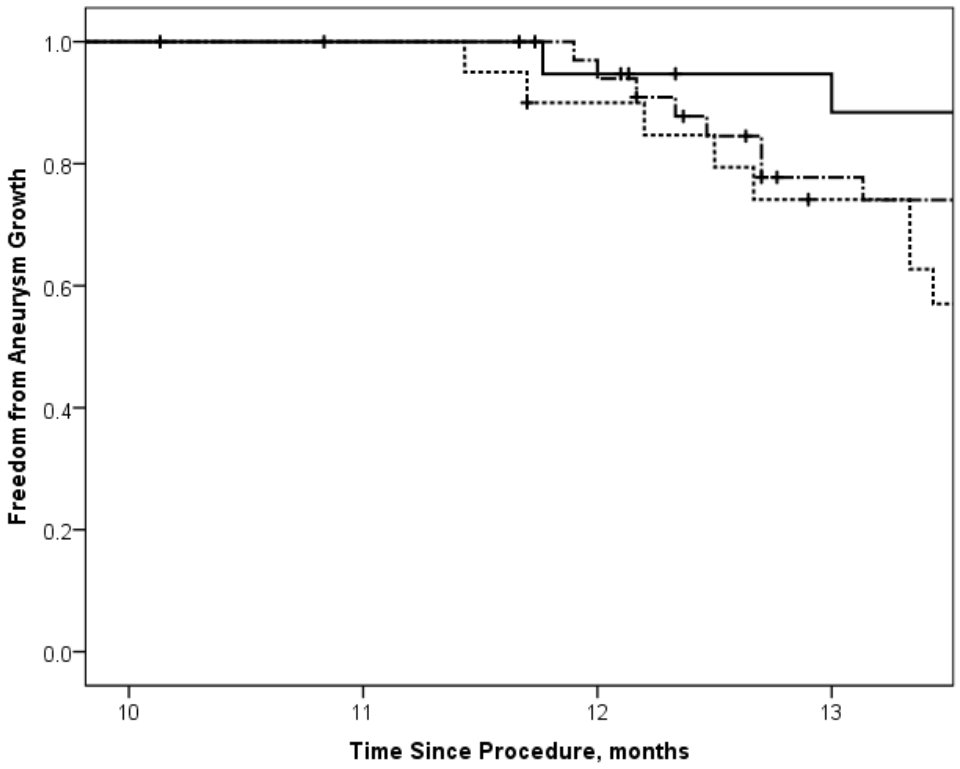


Table 8. 11 Survival Table of freedom from proximal displacement

Survival Table

	Time	Status	Cumulative Proportion Surviving at the Time		N of Cumulative Events	N of Remaining Cases
			Estimate	Std. Error		
1	304.000	.00	.	.	0	75
2	325.000	1.00	.987	.013	1	74
3	332.000	1.00	.973	.019	2	73
4	350.000	.00	.	.	2	72
5	351.000	.00	.	.	2	71
6	351.000	.00	.	.	2	70
7	352.000	1.00	.959	.023	3	69
8	357.000	1.00	.946	.026	4	68
9	360.000	.00	.	.	4	67
10	363.000	1.00	.	.	5	66
11	363.000	1.00	.917	.032	6	65
12	364.000	.00	.	.	6	64
13	365.000	1.00	.903	.035	7	63
14	366.000	.00	.	.	7	62
15	370.000	1.00	.	.	8	61
16	370.000	1.00	.874	.039	9	60
17	371.000	1.00	.859	.041	10	59
18	374.000	1.00	.845	.043	11	58
19	377.000	1.00	.830	.045	12	57
20	379.000	1.00	.816	.046	13	56
21	381.000	1.00	.801	.048	14	55
22	381.000	.00	.	.	14	54
23	383.000	.00	.	.	14	53
24	386.000	1.00	.786	.049	15	52
25	387.000	.00	.	.	15	51
26	390.000	1.00	.770	.051	16	50
27	394.000	1.00	.755	.052	17	49
28	395.000	1.00	.740	.053	18	48
29	403.000	1.00	.724	.054	19	47
30	408.000	.00	.	.	19	46
31	408.000	.00	.	.	19	45
32	410.000	1.00	.708	.055	20	44
33	412.000	1.00	.692	.056	21	43
34	421.000	.00	.	.	21	42
35	425.000	1.00	.676	.057	22	41

36	433.000	1.00	.659	.058	23	40
37	441.000	1.00	.643	.059	24	39
38	447.000	.00	.	.	24	38
39	487.000	1.00	.626	.060	25	37
40	577.000	1.00	.609	.061	26	36
41	679.000	1.00	.592	.061	27	35
42	680.000	.00	.	.	27	34
43	688.000	.00	.	.	27	33
44	700.000	.00	.	.	27	32
45	710.000	1.00	.573	.062	28	31
46	713.000	.00	.	.	28	30
47	714.000	1.00	.554	.063	29	29
48	714.000	.00	.	.	29	28
49	715.000	.00	.	.	29	27
50	718.000	.00	.	.	29	26
51	728.000	1.00	.533	.064	30	25
52	731.000	1.00	.	.	31	24
53	731.000	1.00	.490	.066	32	23
54	732.000	1.00	.469	.066	33	22
55	734.000	1.00	.448	.066	34	21
56	735.000	.00	.	.	34	20
57	737.000	.00	.	.	34	19
58	751.000	1.00	.424	.067	35	18
59	760.000	.00	.	.	35	17
60	767.000	.00	.	.	35	16
61	780.000	.00	.	.	35	15
62	784.000	.00	.	.	35	14
63	784.000	.00	.	.	35	13
64	867.000	1.00	.392	.069	36	12
65	970.000	.00	.	.	36	11
66	1045.000	.00	.	.	36	10
67	1079.000	1.00	.352	.073	37	9
68	1087.000	.00	.	.	37	8
69	1092.000	.00	.	.	37	7
70	1098.000	1.00	.302	.078	38	6
71	1106.000	.00	.	.	38	5
72	1115.000	.00	.	.	38	4
73	1126.000	1.00	.227	.088	39	3
74	1131.000	1.00	.151	.085	40	2
75	1156.000	1.00	.076	.068	41	1

76	1176.000	1.00	.000	.000	42	0

Table 8. 12 Survival Table of freedom from migration

Survival Table

	Time	Status	Cumulative Proportion Surviving at the Time		N of Cumulative Events	N of Remaining Cases
			Estimate	Std. Error		
1	304.000	.00	.	.	0	75
2	325.000	1.00	.987	.013	1	74
3	350.000	.00	.	.	1	73
4	351.000	.00	.	.	1	72
5	351.000	.00	.	.	1	71
6	352.000	.00	.	.	1	70
7	360.000	.00	.	.	1	69
8	363.000	.00	.	.	1	68
9	364.000	.00	.	.	1	67
10	365.000	1.00	.972	.020	2	66
11	366.000	.00	.	.	2	65
12	370.000	.00	.	.	2	64
13	371.000	.00	.	.	2	63
14	374.000	.00	.	.	2	62
15	379.000	.00	.	.	2	61
16	381.000	1.00	.956	.025	3	60
17	381.000	.00	.	.	3	59
18	383.000	.00	.	.	3	58
19	387.000	.00	.	.	3	57
20	390.000	.00	.	.	3	56
21	394.000	.00	.	.	3	55
22	403.000	.00	.	.	3	54
23	408.000	.00	.	.	3	53
24	408.000	.00	.	.	3	52
25	410.000	.00	.	.	3	51
26	412.000	1.00	.937	.031	4	50
27	421.000	.00	.	.	4	49
28	441.000	.00	.	.	4	48
29	447.000	.00	.	.	4	47
30	487.000	1.00	.917	.036	5	46
31	577.000	.00	.	.	5	45
32	680.000	.00	.	.	5	44
33	688.000	.00	.	.	5	43
34	700.000	.00	.	.	5	42

35	707.000	.00	.	.	5	41
36	710.000	.00	.	.	5	40
37	713.000	.00	.	.	5	39
38	714.000	.00	.	.	5	38
39	714.000	.00	.	.	5	37
40	715.000	.00	.	.	5	36
41	718.000	.00	.	.	5	35
42	728.000	.00	.	.	5	34
43	731.000	.00	.	.	5	33
44	732.000	.00	.	.	5	32
45	734.000	.00	.	.	5	31
46	735.000	.00	.	.	5	30
47	737.000	.00	.	.	5	29
48	740.000	1.00	.886	.047	6	28
49	751.000	1.00	.854	.055	7	27
50	760.000	1.00	.822	.061	8	26
51	760.000	.00	.	.	8	25
52	767.000	.00	.	.	8	24
53	780.000	.00	.	.	8	23
54	783.000	1.00	.787	.068	9	22
55	784.000	.00	.	.	9	21
56	784.000	.00	.	.	9	20
57	803.000	1.00	.747	.075	10	19
58	805.000	.00	.	.	10	18
59	867.000	1.00	.706	.082	11	17
60	970.000	.00	.	.	11	16
61	1045.000	.00	.	.	11	15
62	1065.000	1.00	.659	.089	12	14
63	1078.000	.00	.	.	12	13
64	1087.000	.00	.	.	12	12
65	1091.000	.00	.	.	12	11
66	1092.000	.00	.	.	12	10
67	1098.000	.00	.	.	12	9
68	1106.000	.00	.	.	12	8
69	1115.000	.00	.	.	12	7
70	1176.000	.00	.	.	12	6
71	1334.000	1.00	.549	.125	13	5
72	1443.000	1.00	.439	.140	14	4
73	1456.000	1.00	.329	.142	15	3
74	1457.000	1.00	.220	.130	16	2

75	1465.000	.00	.	.	16	1
76	1490.000	.00	.	.	16	0

Table 8. 13 Survival Table of freedom from proximal displacement in different IFU groups

IFU groups: (1) *IFU-2016 compliant; (2) IFU-2013 compliant (Non-compliant with IFU-2016); (3) Non-compliant with IFU-2013 and IFU-2016.*

Survival Table

IFUGROUPS		Time	Status	Cumulative Proportion Surviving at the Time		N of Cumulative Events	N of Remaining Cases
				Estimate	Std. Error		
1.00	1	351.000	.00	.	.	0	19
	2	351.000	.00	.	.	0	18
	3	366.000	.00	.	.	0	17
	4	387.000	.00	.	.	0	16
	5	403.000	1.00	.938	.061	1	15
	6	408.000	.00	.	.	1	14
	7	421.000	.00	.	.	1	13
	8	425.000	1.00	.865	.089	2	12
	9	487.000	1.00	.793	.107	3	11
	10	688.000	.00	.	.	3	10
	11	710.000	1.00	.714	.122	4	9
	12	713.000	.00	.	.	4	8
	13	715.000	.00	.	.	4	7
	14	760.000	.00	.	.	4	6
	15	970.000	.00	.	.	4	5
	16	1092.000	.00	.	.	4	4
	17	1106.000	.00	.	.	4	3
	18	1115.000	.00	.	.	4	2
	19	1126.000	1.00	.357	.260	5	1
	20	1176.000	1.00	.000	.000	6	0
2.00	1	325.000	1.00	.971	.028	1	34
	2	350.000	.00	.	.	1	33
	3	357.000	1.00	.942	.040	2	32
	4	360.000	.00	.	.	2	31
	5	363.000	1.00	.912	.049	3	30
	6	365.000	1.00	.881	.056	4	29
	7	370.000	1.00	.851	.062	5	28
	8	371.000	1.00	.820	.066	6	27
	9	374.000	1.00	.790	.071	7	26
	10	379.000	1.00	.760	.074	8	25
	11	381.000	1.00	.729	.077	9	24
	12	381.000	.00	.	.	9	23

	13	383.000	.00	.	.	9	22
	14	386.000	1.00	.696	.080	10	21
	15	394.000	1.00	.663	.083	11	20
	16	395.000	1.00	.630	.085	12	19
	17	408.000	.00	.	.	12	18
	18	412.000	1.00	.595	.088	13	17
	19	433.000	1.00	.560	.089	14	16
	20	577.000	1.00	.525	.090	15	15
	21	679.000	1.00	.490	.091	16	14
	22	700.000	.00	.	.	16	13
	23	714.000	1.00	.452	.091	17	12
	24	714.000	.00	.	.	17	11
	25	718.000	.00	.	.	17	10
	26	728.000	1.00	.407	.093	18	9
	27	731.000	1.00	.362	.093	19	8
	28	734.000	1.00	.317	.091	20	7
	29	767.000	.00	.	.	20	6
	30	784.000	.00	.	.	20	5
	31	867.000	1.00	.253	.093	21	4
	32	1087.000	.00	.	.	21	3
	33	1098.000	1.00	.169	.092	22	2
	34	1131.000	1.00	.084	.076	23	1
	35	1156.000	1.00	.000	.000	24	0
3.00	1	304.000	.00	.	.	0	20
	2	332.000	1.00	.950	.049	1	19
	3	352.000	1.00	.900	.067	2	18
	4	363.000	1.00	.850	.080	3	17
	5	364.000	.00	.	.	3	16
	6	370.000	1.00	.797	.091	4	15
	7	377.000	1.00	.744	.099	5	14
	8	390.000	1.00	.691	.105	6	13
	9	410.000	1.00	.638	.110	7	12
	10	441.000	1.00	.584	.113	8	11
	11	447.000	.00	.	.	8	10
	12	680.000	.00	.	.	8	9
	13	731.000	1.00	.519	.117	9	8
	14	732.000	1.00	.455	.119	10	7
	15	735.000	.00	.	.	10	6
	16	737.000	.00	.	.	10	5
	17	751.000	1.00	.364	.125	11	4

	18	780.000	.00	.	.	11	3
	19	784.000	.00	.	.	11	2
	20	1045.000	.00	.	.	11	1
	21	1079.000	1.00	.000	.000	12	0

Table 8. 14 Log rank results of proximal displacement in different IFU groups

Log Rank (Mantel – Cox)	IFU-2016 Compliant		IFU-2013 compliant (Non-compliant with IFU-2016)		*Non-compliant with IFU-2013 and IFU-2016*	
	X^2	P value	X^2	P value	X^2	P value
IFU-2016 Compliant			7.592	0. 006	5.350	0.021
IFU-2013 compliant (Non-compliant with IFU-2016)	7.592	0.006			0.081	0.775
Non-compliant with IFU-2013 and IFU-2016	5.350	0.021	.081	0.775		

Figure 8. 2 Freedom from proximal displacement in different IFU groups (Cut off at SE>10%)

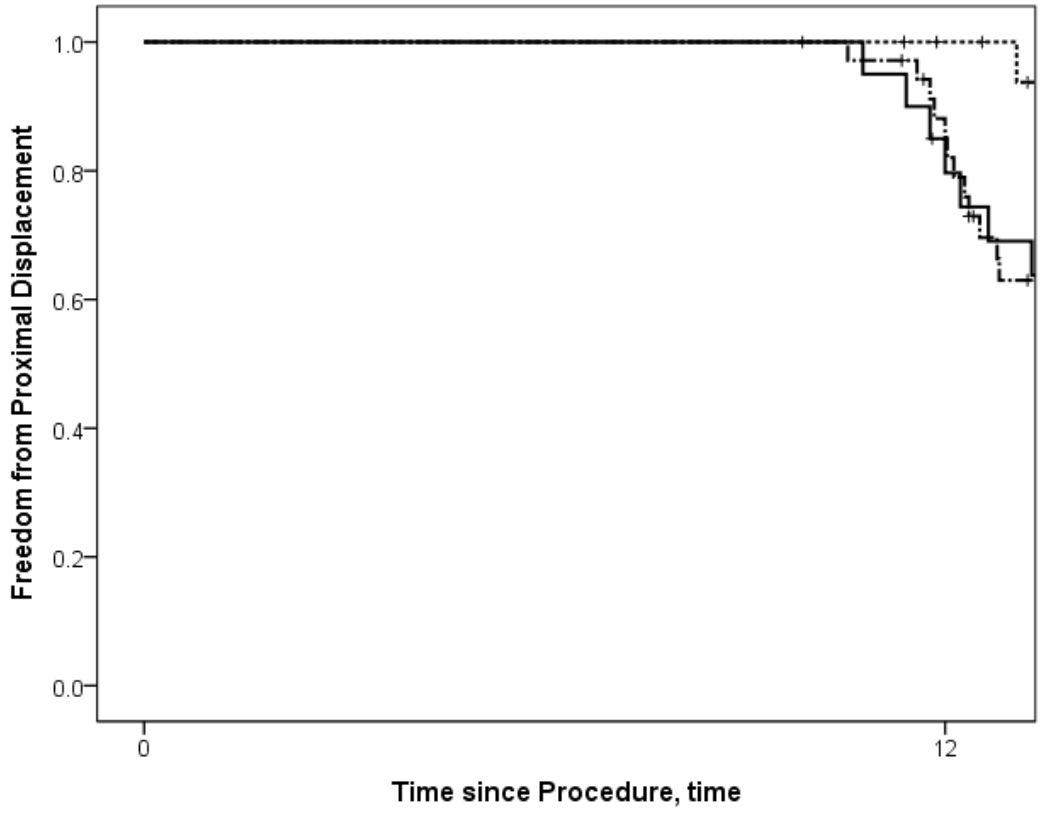


Table 8. 15 Survival Table of freedom from migration in different IFU groups

Survival Table

IFUGROUPS		Time	Status	Cumulative Proportion Surviving at the Time		N of Cumulative Events	N of Remaining Cases
				Estimate	Std. Error		
1.00	1	351.000	.00	.	.	0	19
	2	351.000	.00	.	.	0	18
	3	366.000	.00	.	.	0	17
	4	387.000	.00	.	.	0	16
	5	403.000	.00	.	.	0	15
	6	408.000	.00	.	.	0	14
	7	421.000	.00	.	.	0	13
	8	487.000	1.00	.923	.074	1	12
	9	688.000	.00	.	.	1	11
	10	710.000	.00	.	.	1	10
	11	713.000	.00	.	.	1	9
	12	714.000	.00	.	.	1	8
	13	715.000	.00	.	.	1	7
	14	760.000	.00	.	.	1	6
	15	970.000	.00	.	.	1	5
	16	1092.000	.00	.	.	1	4
	17	1106.000	.00	.	.	1	3
	18	1115.000	.00	.	.	1	2
	19	1176.000	.00	.	.	1	1
	20	1456.000	1.00	.000	.000	2	0
2.00	1	325.000	1.00	.971	.028	1	34
	2	350.000	.00	.	.	1	33
	3	360.000	.00	.	.	1	32
	4	365.000	1.00	.941	.040	2	31
	5	371.000	.00	.	.	2	30
	6	374.000	.00	.	.	2	29
	7	379.000	.00	.	.	2	28
	8	381.000	1.00	.907	.051	3	27
	9	381.000	.00	.	.	3	26
	10	383.000	.00	.	.	3	25
	11	394.000	.00	.	.	3	24
	12	408.000	.00	.	.	3	23
	13	412.000	1.00	.868	.062	4	22
	14	577.000	.00	.	.	4	21

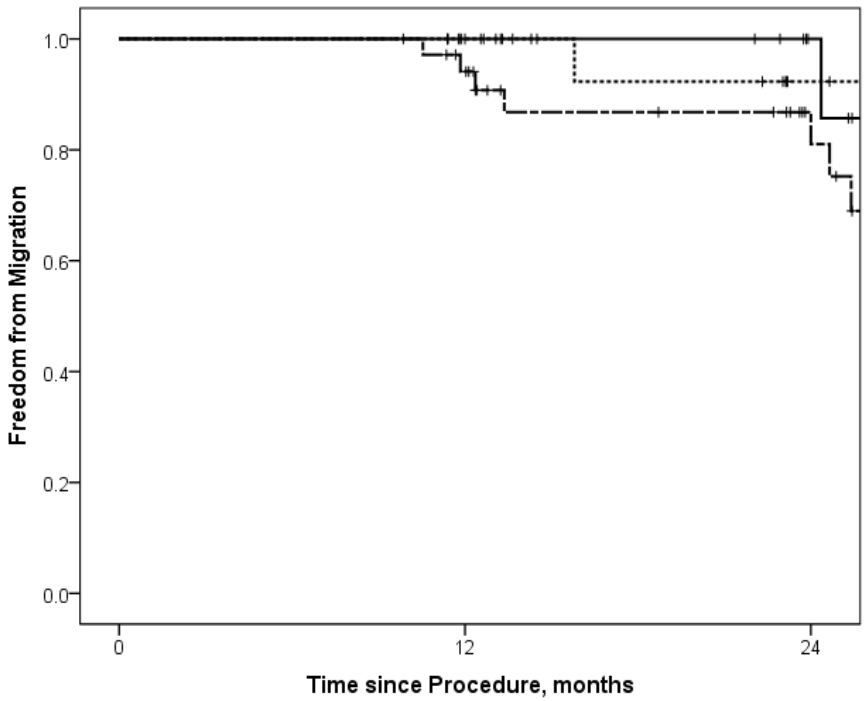
	15	700.000	.00	.	.	4	20
	16	714.000	.00	.	.	4	19
	17	718.000	.00	.	.	4	18
	18	728.000	.00	.	.	4	17
	19	731.000	.00	.	.	4	16
	20	734.000	.00	.	.	4	15
	21	740.000	1.00	.810	.081	5	14
	22	760.000	1.00	.752	.093	6	13
	23	767.000	.00	.	.	6	12
	24	783.000	1.00	.690	.105	7	11
	25	784.000	.00	.	.	7	10
	26	805.000	.00	.	.	7	9
	27	867.000	1.00	.613	.118	8	8
	28	1065.000	1.00	.536	.125	9	7
	29	1078.000	.00	.	.	9	6
	30	1087.000	.00	.	.	9	5
	31	1098.000	.00	.	.	9	4
	32	1334.000	1.00	.402	.149	10	3
	33	1443.000	1.00	.268	.148	11	2
	34	1465.000	.00	.	.	11	1
	35	1490.000	.00	.	.	11	0
3.00	1	304.000	.00	.	.	0	20
	2	352.000	.00	.	.	0	19
	3	363.000	.00	.	.	0	18
	4	364.000	.00	.	.	0	17
	5	370.000	.00	.	.	0	16
	6	390.000	.00	.	.	0	15
	7	410.000	.00	.	.	0	14
	8	441.000	.00	.	.	0	13
	9	447.000	.00	.	.	0	12
	10	680.000	.00	.	.	0	11
	11	707.000	.00	.	.	0	10
	12	732.000	.00	.	.	0	9
	13	735.000	.00	.	.	0	8
	14	737.000	.00	.	.	0	7
	15	751.000	1.00	.857	.132	1	6
	16	780.000	.00	.	.	1	5
	17	784.000	.00	.	.	1	4
	18	803.000	1.00	.643	.210	2	3
	19	1045.000	.00	.	.	2	2

	20	1091.000	.00	.	.	2	1
	21	1457.000	1.00	.000	.000	3	0

Table 8. 16 Log rank results of migration in different IFU groups

Log Rank (Mantel – Cox)	IFU-2016 Compliant		IFU-2013 compliant (Non-compliant with IFU-2016)		*Non-compliant with IFU-2013 and IFU-2016*	
	X^2	P value	X^2	P value	X^2	P value
IFU-2016 Compliant			2.011	0.156	0.015	0.904
IFU-2013 compliant (Non-compliant with IFU-2016)	2.011	0.156			0.510	0.475
Non-compliant with IFU-2013 and IFU-2016	0.015	0.904	0.510	0.475		

Figure 8. 3 Freedom from migration in different IFU groups (Cut off at SE>10%)

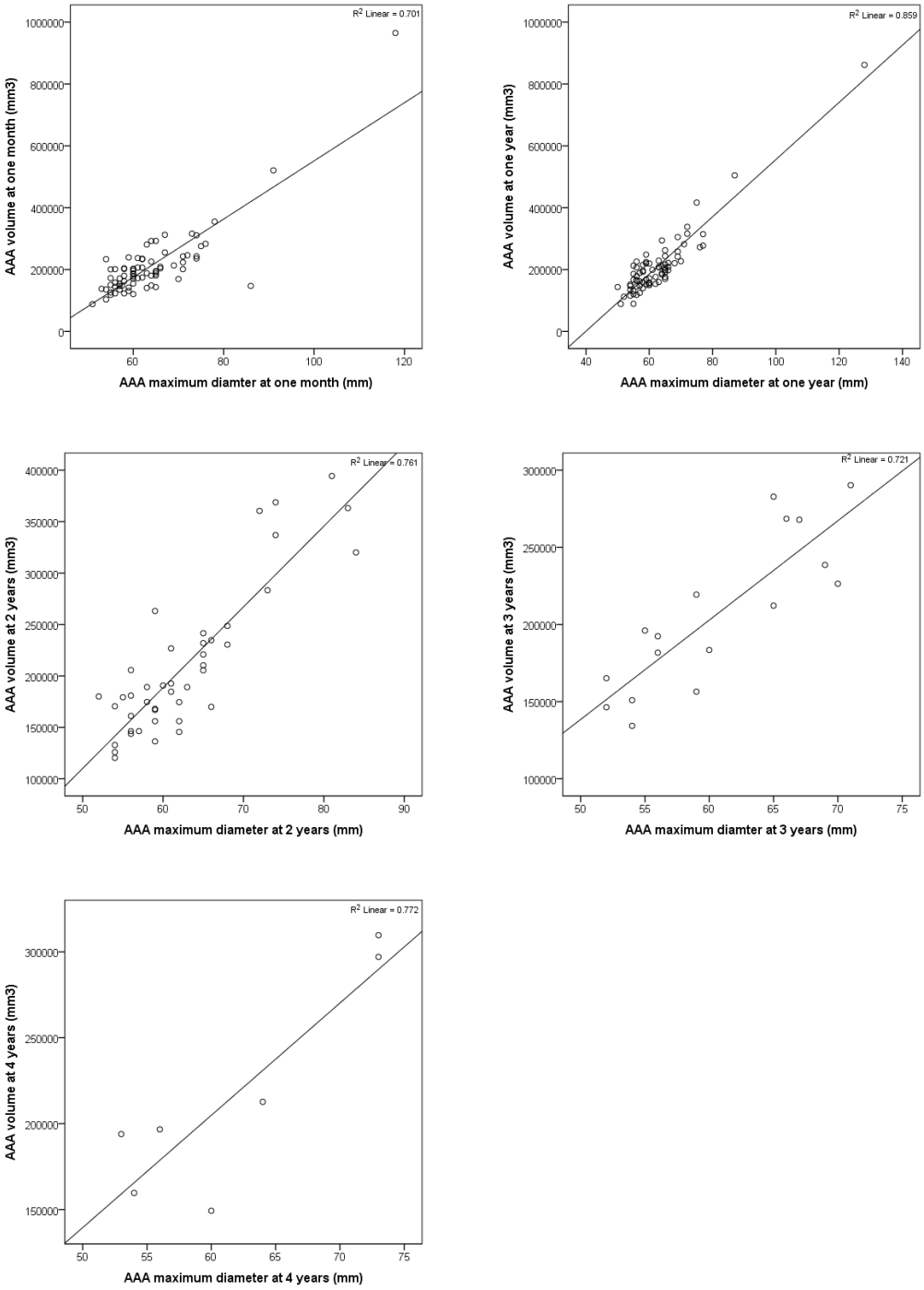


8.4. Diameter vs Volume

Table 8. 17 Pearson correlation of AAA volume x AAA maximum diameter at each time point

Time	Pearson correlation	P value
One month	0.837	0.000
One year	0.927	0.000
Two years	0.872	0.000
Three years	0.849	0.000
Four years	0.878	0.009

Figure 8. 4 Scatter plot of AAA volume x AAA maximum diameter at each time point



8.5. Linear Mixed Model

Step 1: Unconditional Mean Model (Model 1)

Table 8. 18 Model 1: Information Criteria[a]

-2 Log Likelihood	2334.620
Akaike's Information Criterion (AIC)	2340.620
Hurvich and Tsai's Criterion (AICC)	2340.731
Bozdogan's Criterion (CAIC)	2353.815
Schwarz's Bayesian Criterion (BIC)	2350.815

The information criteria are displayed in smaller-is-better form.

a. Dependent Variable: AAA volume.

Table 8. 19 Model 1: Estimates of Fixed Effects[a]

						95% Confidence Interval	
Parameter	Estimate	Std. Error	df	t	Sig.	Lower Bound	Upper Bound
Intercept	216.154661	12.005293	75.327	18.005	.000	192.240593	240.068729

a. Dependent Variable: AAA volume.

Table 8. 20 Model 1: Estimates of Covariance Parameters[a]

						95% Confidence Interval	
Parameter		Estimate	Std. Error	Wald Z	Sig.	Lower Bound	Upper Bound
Residual		581.363271	68.436166	8.495	.000	461.579969	732.231197
Intercept [subject = id]	Variance	10735.107612	1785.129466	6.014	.000	7749.273978	14871.397729

a. Dependent Variable: AAA volume.

Intraclass correlation coefficient (ICC) = 10735/(10735+581) = 0.94866

Step 2: Unconditional Linear Growth Curve Model (Model 2)

Table 8. 21 Model 2: Information Criteria[a]

-2 Log Likelihood	2248.888
Akaike's Information Criterion (AIC)	2260.888
Hurvich and Tsai's Criterion (AICC)	2261.280
Bozdogan's Criterion (CAIC)	2287.277
Schwarz's Bayesian Criterion (BIC)	2281.277

The information criteria are displayed in smaller-is-better form.

a. Dependent Variable: AAA volume.

Table 8. 22 Model 2: Estimates of Fixed Effects[a]

						95% Confidence Interval	
Parameter	Estimate	Std. Error	df	t	Sig.	Lower Bound	Upper Bound
Intercept	196.201040	13.462080	72.237	14.574	.000	169.366379	223.035701
Time	9.366164	2.184228	45.321	4.288	.000	4.967763	13.764565

a. Dependent Variable: AAA volume.

Table 8. 23 Model 2: Estimates of Covariance Parameters[a]

						95% Confidence Interval	
Parameter		Estimate	Std. Error	Wald Z	Sig.	Lower Bound	Upper Bound
Residual		175.074763	31.541330	5.551	.000	122.990554	249.215666
Intercept + Time [subject = id]	UN (1,1)	13316.948237	2296.737156	5.798	.000	9497.304021	18672.784399
	UN (2,1)	-921.364319	364.530602	-2.528	.011	-1635.831169	-206.897468
	UN (2,2)	235.647320	76.285387	3.089	.002	124.941187	444.446389

a. Dependent Variable: AAA volume.

Step 3: Quadratic Growth Curve Model (Higher-Order Change Trajectories) (Model 3)

Table 8. 24 Model 3: Information Criteria[a]

-2 Log Likelihood	2223.140
Akaike's Information Criterion (AIC)	2237.140
Hurvich and Tsai's Criterion (AICC)	2237.666
Bozdogan's Criterion (CAIC)	2267.927
Schwarz's Bayesian Criterion (BIC)	2260.927

The information criteria are displayed in smaller-is-better form.

a. Dependent Variable: AAA volume.

Table 8. 25 Model 3: Estimates of Fixed Effects[a]

						95% Confidence Interval	
Parameter	Estimate	Std. Error	df	t	Sig.	Lower Bound	Upper Bound
Intercept	213.461511	13.678460	81.167	15.606	.000	186.246516	240.676505
Time	-9.849463	4.031823	128.035	-2.443	.016	-17.827093	-1.871832
Time^2	4.531265	.810940	83.694	5.588	.000	2.918537	6.143993

a. Dependent Variable: AAA volume.

Table 8. 26 Model 3: Estimates of Covariance Parameters[a]

						95% Confidence Interval	
Parameter		Estimate	Std. Error	Wald Z	Sig.	Lower Bound	Upper Bound
Residual		119.646740	21.685282	5.517	.000	83.873641	170.677489
Intercept + Time [subject = id]	UN (1,1)	13206.454365	2239.494636	5.897	.000	9472.030328	18413.205074
	UN (2,1)	-918.131730	339.841552	-2.702	.007	-1584.208933	-252.054528
	UN (2,2)	274.366325	72.782949	3.770	.000	163.127434	461.460578

a. Dependent Variable: AAA volume.

Step 4: Cubic Growth Curve Model (Higher-Order Change Trajectories) (Model 4)

Table 8. 27 Model 4: Information Criteria[a]

-2 Log Likelihood	2217.347
Akaike's Information Criterion (AIC)	2233.347
Hurvich and Tsai's Criterion (AICC)	2234.026
Bozdogan's Criterion (CAIC)	2268.532
Schwarz's Bayesian Criterion (BIC)	2260.532

The information criteria are displayed in smaller-is-better form.

a. Dependent Variable: AAA volume.

Table 8. 28 Model 4: Estimates of Fixed Effects[a]

						95% Confidence Interval	
Parameter	Estimate	Std. Error	df	t	Sig.	Lower Bound	Upper Bound
Intercept	231.468638	15.458210	122.334	14.974	.000	200.868405	262.068871
Time	-37.781041	12.011795	76.641	-3.145	.002	-61.701368	-13.860715
Time^2	16.557427	4.955564	73.041	3.341	.001	6.681095	26.433759
Time^3	-1.475189	.601337	70.988	-2.453	.017	-2.674224	-.276153

a. Dependent Variable: AAA volume.

Table 8. 29 Model 4: Estimates of Covariance Parameters[a]

						95% Confidence Interval	
Parameter		Estimate	Std. Error	Wald Z	Sig.	Lower Bound	Upper Bound
Residual		110.695619	20.184776	5.484	.000	77.431596	158.249610
Intercept + Time [subject = id]	UN (1,1)	13154.349286	2224.309147	5.914	.000	9443.589433	18323.213474
	UN (2,1)	-895.317726	333.179518	-2.687	.007	-1548.337581	-242.297872
	UN (2,2)	276.543132	71.687814	3.858	.000	166.382376	459.640652

a. Dependent Variable: AAA volume.

Step 5: Adding Potential Predictors (Model 5)

Table 8. 30 Model 5: Information Criteria[a]

-2 Log Likelihood	2197.492
Akaike's Information Criterion (AIC)	2227.492
Hurvich and Tsai's Criterion (AICC)	2229.834
Bozdogan's Criterion (CAIC)	2293.465
Schwarz's Bayesian Criterion (BIC)	2278.465

The information criteria are displayed in smaller-is-better form.

a. Dependent Variable: AAA volume.

Table 8. 31 Model 5: Estimates of Fixed Effects[a]

						95% Confidence Interval	
Parameter	Estimate	Std. Error	df	t	Sig.	Lower Bound	Upper Bound
Intercept	432.014311	153.460800	73.995	2.815	.006	126.236656	737.791966
Time	-37.281785	11.950914	78.485	-3.120	.003	-61.071911	-13.491659
Time^2	16.342388	4.927925	74.742	3.316	.001	6.524903	26.159873
Time^3	-1.454499	.598010	72.646	-2.432	.017	-2.646430	-.262568
Age	-1.668147	1.414615	73.322	-1.179	.242	-4.487261	1.150968
Neck Angle	-1.136889	.648688	73.010	-1.753	.084	-2.429719	.155941
Neck Diameter	5.651240	2.019639	72.421	2.798	.007	1.625564	9.676916
Neck Length	-.906380	.876127	71.203	-1.035	.304	-2.653242	.840482
ratio of maximum AAA diameter to maximum AAA lumen diameter	-27.394479	20.181770	71.098	-1.357	.179	-67.634826	12.845869
Proximal displacement	-7.427173	24.602246	72.733	-.302	.764	-56.462416	41.608070
Migration	62.183027	29.099272	72.198	2.137	.036	4.177411	120.188642

a. Dependent Variable: AAA volume.

Table 8. 32 Model 5: Estimates of Covariance Parameters[a]

Parameter		Estimate	Std. Error	Wald Z	Sig.	95% Confidence Interval	
						Lower Bound	Upper Bound
Residual		109.529487	19.729090	5.552	.000	76.949830	155.902987
Intercept + Time [subject = id]	UN (1,1)	11143.426737	1898.922972	5.868	.000	7979.352937	15562.159041
	UN (2,1)	-981.037898	314.165606	-3.123	.002	-1596.791171	-365.284624
	UN (2,2)	283.459691	71.987921	3.938	.000	172.313249	466.298424

a. Dependent Variable: AAA volume.